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GENERAL

Five years' work of the Commission on Narcotic Drugs

By Prof. H. Laugier

After working five years as Assistant Secretary-General in charge of the Department of Social Affairs, Professor Laugier has left the United Nations Secretariat. He did not want to leave without participating once more in the work of the Commission on Narcotic Drugs in which he always took a keen interest. Here is how he summed up his view of its activities:

This is the last time that I shall have the honour to address the Commission on Narcotic Drugs in my capacity as representative of the Secretary-General, and I should like on this occasion to express my appreciation of all that has been accomplished by this Commission in less than five years. When I rose to speak at the first session of the United Nations Commission on Narcotic Drugs, I did not dare to hope that on the expiry of my term of office I would be able to look back with such satisfaction over the road we have travelled. I do not say that all is for the best in the world of narcotic drugs, I do not say that you have solved all the problems with which you were faced: I say only that significant and important results have been achieved.

Let us now consider together the progress we have made in the years between 1946 and 1951. At the end of the Second World War, after those years in which humanitarian problems had taken a secondary place in the thoughts of the Allied Powers driven by necessity into a merciless struggle against nazi aggression, amidst the physical and mental anguish of the war victims and in the disorganized state of international thought and life, traffickers in narcotic drugs enjoyed ideal conditions for their operations. It was urgently necessary to restore international co-operation in this field, as in all the devastated lands of Europe and among all the nations of the world. It was for this reason that the United Nations General Assembly and the Economic and Social Council set up a body, this Commission, which set to work with a profound awareness of its lofty responsibilities.

Fifteen States were designated to constitute your Commission and for that purpose pursued a policy for which they cannot be too highly commended: they selected representatives who were highly qualified technically for what was a technical task. That is why, as a doctor and physiologist, I have always felt perfectly at home in this Commission, as though at a meeting of my colleagues.

By your practical and fruitful discussions you have gained an outstanding place in the vast army of international agencies, a place which you have won by virtue of your expert knowledge, your competence and your hard, unremitting and creative work.

In 1946 the Commission's prime task was to re-establish control, a field in which the universally acknowledged success of the League of Nations was hard to live up to. The first step therefore was the signature of the 1946 Protocol which provided a solid legal basis for the transfer to the United Nations of the functions and powers previously belonging to the League of Nations.

It was then necessary to re-establish relations with international agencies, including the Permanent Central Opium Board and the Supervisory Body, and with governments, so that the painful efforts of the two previous decades should not have been made in vain. This has been accomplished: the annual reports, the seizure reports, and the laws and regulations of the various countries are now circulated once more to all the departments concerned through the agency of an international Secretariat which studies them and extracts the information they contain.

With the re-establishment of international exchanges, however, the world came face to face with the interrelated problems of drug addiction and illicit traffic which for forty years have hindered international agreement and co-operation. In dealing with these two problems, you have acted, not as a world government might have done, by enacting universal laws, but by making use, on the one hand, of the effective means made available by the Conventions, and, on the other hand, of public opinion, that powerful and formidable weapon which, happily, is used from time to time in the interests of mankind. Drug addiction may be studied, it may be cured, but it cannot, as such, be legislated out of existence. That is why you have emphasized the need to improve living conditions and, above all, educational facilities in those countries in which drug addiction is rife. You have combated the illicit traffic which foments this evil by recommending legal penalties for traffickers and by help-

ing governments to acquire a better technical knowledge of the traffic. I should like to illustrate this by reference to the programme of research now in full swing to determine the origin of opium by chemical and physical means. This experiment provides a specific example of international co-operation; though limited in scope, it is important as representing one of the first steps towards collective scientific action to combat a scourge of mankind.

You have not confined yourselves, however, to applying the principles laid down in the Conventions; in following the course of events you have gone beyond the mere letter of those Conventions. A number of governments, for example, have been given effective technical assistance in reorganizing their national drug-control services; progress has been made with the attempt to abolish opium smoking in the Far East; above all, synthetic drugs have been placed under control and prevented, so to speak, at birth from having injurious effects. The Paris Protocol is undoubtedly one of the most important technical achievements standing to the credit of the United Nations.

And now you are faced at the present time with fresh problems of great complexity, the solutions of which will have more than technical results: they pave the way, I feel, to the kind of action which the Members of the United Nations hoped to see accomplished while the war was raging—truly disinterested collective action whereby every nation surrendered something of its sovereignty, that is to say, of its power and pride, for the sake of international co-operation. The action I have in mind is the limitation of the production of raw materials. I have read and carefully studied the report of the Commission of Enquiry on the Coca Leaf. As a doctor, and simply as a friend of humanity, I have found this report extremely interesting and have been struck by the practical possibilities afforded by international action to improve the lot of those nations which, by historical or geographical accident, have become under-privileged. It is a great task that you have undertaken and I am confident that it will be extended and successfully completed in the next few years.

At this session you are going to discuss the problems raised by another important raw material—opium. Here, too, your work may literally be revolutionary, since what is called for is not the uttering of verbal exorcisms nor the formulation of pious hopes, but, in the case of a number of countries, the acceptance of a specific, and, in some cases, heavy financial loss in the interest of mankind as a whole. I cannot appeal to you too strongly to succeed in this task, to reach agreement and establish a viable international monopoly which will demonstrate that it is possible for men and governments to subordinate their legitimate national interests to the higher interests of suffering mankind.

In conclusion, I should like to say that although I am leaving you I shall continue to be closely interested in your work. You are about to attempt the drafting of a single Convention which will organize the control of narcotic drugs on a simple and practical basis. When this Convention has been drafted and comes into force I shall be proud to have contributed to it, in however small a degree. I should like to add that five years of work for a cause such as ours leave their mark on a man and that, despite the inevitable disappointments, difficulties and occasional setbacks and, at times, the feeling of being unequal to the task, five years of work cannot become just another memory: they are for me more than an experience, an enrichment; they represent a whole period of my life which will profoundly influence all the efforts I hope still to be able to devote to the great causes for which we have fought together.

The International Criminal Police Commission and the Illicit Traffic of Narcotics

By Paul Marabuto

Representative of the ICPC at the fifth session of the Commission on Narcotic Drugs

The question of suppressing the illicit traffic in narcotic drugs raises various problems on the international plane for the police forces of many countries. To solve these problems, the experience of an international organization of a technical character is of course a great asset. The ICPC, of which thirty-nine nations are members, is the most important among international police institutions. Its original files contain more than 60,000 individual index cards of international criminals. The following article gives an idea of the nature and functions of this organization.

I. How the Idea of International Police Co-operation Germinated and was Carried into Effect

When, in modern times, the question of repression on an international scale arose, two main problems preoccupied the jurists: the unification of international penal law, and extradition. These two preoccupations were inspired by an important principle: the universality of the right to punish, which aims at reaching the malefactor wherever he may be.

Numerous juridical conferences have been held for the purpose of making penal law uniform. Results have been obtained, but we are far from having achieved this unification. The diversity of national legislations is still considerable, both from the point of view of principles and practice.

In this same spirit and parallel to this work of unification, the practice of extradition became generalized. The number of extradition treaties increased in order to check the concept of the right of sanctuary in crimes under the ordinary law and especially in order to pursue the malefactor in his last places of refuge.

Thus, on the one hand, the unification of penal law has not yet been accomplished in a satisfactory way, and on the other, the procedure of extradition encounters difficulties of interpretation and, above all, such tardy progress is incompatible with the development of law against international crime.

Therefore, in the words of a great criminalist: "The internationalism of crime should be opposed by the internationalism of repression."[1]

During all this time, there is a recrudescence of criminality and this progression is encouraged by the development of means of locomotion which are steadily increasing: it takes on an international character, owing to the fact that criminal activity is widespread.

"The increasing facilities of communications, the progress of automobilism, even aviation, have put at the disposal of malefactors a great many means of crossing frontiers which enable them to escape from national police investigations."[2]

"The frontier thus becomes an unsurmountable barrier for the police official and the safety plank for the criminal."[3]

* * *

It was in this atmosphere that the idea of international police co-operation germinated, based on the principle of an exchange of documentation and the cohesion of all forces in the search and pursuit of international malefactors.

It was noticed, indeed, at all the above-mentioned conferences, at penal law congresses and penitentiary congresses, that there were the same gaps, viz., the lack of facilities for the collection and exchange of information and statistics relative to criminals.

The question of closer surveillance of the activities of international criminals and the establishment of more efficient means of opposing them, was put on the agenda of numerous international conferences. Whilst the departments of foreign affairs of the different countries drew up extradition treaties, penitentiary congresses met

in order to examine another aspect of this problem. The first of these conferences took place in Frankfort (Germany), in 1845, and others followed at various intervals until 1930, at which date the last congress was held in Prague.

The Institute of International Legislation had, meanwhile, examined the question on several occasions from the legislative aspect.

But at all these conferences the same defects mentioned above were noticed. However, two attempts were made to fill in these gaps.

In 1904, France took the initiative with a view to an international arrangement, aiming at a more efficient repression of the white-slave trade, the creation in each country of a central office and also the establishment of relations with these organizations for the exchange of all information relative to the white-slave traffic.

In 1910, a second Convention concerning obscene publications recommended also the setting up of central offices.

* * *

The police had to extend the principle of centralization to all international crime and to undertake a truly efficacious work. It was at this period that the international police came into being.

In April 1914, the First International Congress of Judicial Police was held in the Principality of Monaco. Mr. Larnaude, Dean of the Paris Law School, was president. Eminent police officials and jurists furnished the support of their high authority, by pooling their technical knowledge and experience, in order to accomplish a work of solidarity.

The task of this Congress was indicated by the opinions expressed during their work:

"The International Judicial Police Congress expresses the wish to see direct official contacts between the police forces of the different countries generalized and improved so as to enable investigations of a nature to facilitate the action of penal justice."

At these police meetings twenty-four countries were represented, belonging not only to Europe, but also to America (Brazil, Cuba, Guatemala, San Salvador) and to Asia (Turkey, Persia). The Congress was attended by 300 persons.

The aim, according to the speech made by Mr. Larnaude, was "to facilitate and make more rapid the arrests of criminals wherever they were".

The following questions were on the agenda: extradition, improvement of the identification system, international criminal records, questions relating to police technique.

Unfortunately, the war in 1914 disorganized these efforts. The absence of normal relations until 1918 and the defence of national safety prevented the continuation of a work devoted to general welfare. Therefore, the police congress which should have taken place in 1916 in Bucarest, could not be held.

The outbreak of war had, however, a favourable influence; by rendering communications between nations slower and more complicated and by tightening up regulations, it subjected the movements of criminals to strict control which hindered their traffic considerably.

This traffic came back to normal after the war, with greater intensity owing to the fact that during this troubled period there had been numerous new inventions which had increased facilities for travelling and correspondence.

Thus the impulsion given to the Congress of Monaco, had been only temporarily broken. A work commenced under good auspices could not remain unaccomplished.

About ten years later, a second International Judicial Police Conference was held in Vienna, on the initiative of Mr. Hans Schober, President of the Police.

From then on, the international police under this great chief received an impulsion quite special, thanks to the creation of a new organization: the International Criminal Police Commission. This creation marked the beginning of the truly active phase, for this department was to maintain this activity in its relations with the various national police departments.

It was in this town that the head office of ICPC was located.

The Commission gave a profound and lasting impulsion to the international services in the struggle against common law crimes.

A whole organization was formed and developed, to which were added numerous services, in particular the International Bureau, which is a central organization for police documentation.

In 1938, the institutions were in full development and the International Criminal Police Commission had already held fourteen sessions, when the Second World War broke out and interrupted their good work.

II. The ICPC and the Organizations belonging to it

The International Criminal Police Commission is the most important organ of international police institutions. In addition to the active members delegated and appointed by various governments, there are also members appointed either because of eminent services rendered to the Commission, or in consideration of their technical or scientific knowledge. It is presided over by Mr. Louwage,

Inspector General of the Belgian Sureté Department, and has seven vice-presidents.

Its creation dates from the Second Judicial Police Congress, held in Vienna in 1923, by virtue of the following resolution:

"Considering the fact that the struggle against international criminality cannot be successfully accomplished without the close co-operation of the police services of all civilized States, the International Police Congress held in Vienna, decides upon the creation of an International Criminal Police Commission which should immediately start to function."

The head office which was before the war in Vienna was transferred in 1946 to Paris, where the International Bureau is also situated. It took up its activities again at the Congress of Brussels (1946).

The mission of the ICPC has two objects: it is entrusted with co-ordinating efforts in view of the struggle against criminality and, in addition, has the task of creating and developing services likely to efficiently assist this struggle.

It is clearly specified in article I of the statutes:

"The purpose of the International Criminal Police Commission is to ensure and officially promote the growth of the greatest possible mutual assistance between all criminal police authorities within the limits of the laws existing in the different States, to establish and develop all institutions likely to contribute to an efficient repression of common law crimes and offences, to the strict exclusion of all matters having a political, religious or racial character."

To assist it in its task, it is aided by an executive committee composed of three general reporters and a Secretary-General. It is an organ of control entrusted with seeing to the execution of all measures adopted by the Assembly, ensuring the functioning of the International Bureau and the preparation of the annual sessions.

It can have recourse to a meeting of reporters among the members of the Commission for the examination of the questions submitted to the Assembly and the elaboration of the reports relative thereto.

The ICPC has met seventeen times since its creation. These meetings take place about every year in a different town.

A number of sub-committees are constituted for the purpose of preparing the study of the problems to which the attention of police officials is drawn during the general assemblies or to facilitate their solution. In this way there are, at the present time, the following sub-committees:

Sub-Committee on Juvenile Delinquency
Sub-Committee on Telecommunications
Sub-Committee on Counterfeiting
Sub-Committee on Statistics
Sub-Committee on Air Police
Sub-Committee on Drugs
Sub-Committee on Scientific and Technical Police

At the head of each sub-committee is an eminent person of the ICPC and its members are chosen from among the other delegates having special competency in the various questions.

Their work is continuous throughout the year and each may meet when it is felt urgent to do so in order to exchange essential points of view.

There are, at the present time, thirty-nine member States of the ICPC:

Argentina
Australia
Austria
Belgium
Bulgaria
Canada
Ceylon
Chile
Czechoslovakia
Denmark
Egypt
Finland
France
Germany (Interallied Zones)
Great Britain
Greece
Guatemala
Hungary
India
Iran
Ireland
Israel
Italy
Lebanon
Luxembourg
Monaco
Norway
The Netherlands & her possessions
Poland
Portugal
Saar
Sweden
Switzerland
Tangiers
Trieste (Anglo-American Zone)
Turkey
Union of South Africa
Venezuela
Yugoslavia

A. THE INTERNATIONAL BUREAU

The International Bureau is the kingpin of the international police institutions. As the executive organ, it is entrusted with the application of the decisions taken during the plenary assemblies, of which it also ensures the preparation (article 2 of the statutes).

It is the hinge which articulates the reception and the transmitting of information concerning international malefactors, for one of the most concrete acts of this co-operation is the exchange of documents between the national offices relative to wanted individuals, or those to be arrested.

Thus it spins the web in which the international malefactor will inevitably become entangled, wherever he may be. Methodical investigations on a universal scale will not lose any time in finding him whilst waiting for the procedure of extradition to start.

Its organization is well worth a little study.

Under the direction of Mr. Ducloux, Secretary-General of the ICPC, it groups a personnel specialized in legal and technical questions and records. It also has translators who are indispensable for the work connected with the *International Review* and for the instructions which are destined for different countries.

With regard to the installation, the International Bureau possesses a section for individual files and criminal documentation. It is fitted up according to the most modern technique.

The General Secretariat of the ICPC has endeavoured to recover the records of the former headquarters in Vienna, which in 1940 were transferred to Berlin by the Germans.

An effort was made to reconstitute the old repertories of international malefactors.

This documentation was established in order to get together as much information as possible relative to identification and inquiries, as also in order to make up for the defects resulting from the lack of elements of identity by creating special files based on morphological peculiarities, and on the speciality of offences, so as to obtain a rational filing system having the greatest value with regard to identification and offering the best guarantees of authenticity.

Several files, therefore, have been constituted with this object:

(*a*) General alphabetical index cards on which all the individuals reported are recorded;

(*b*) Phonetic index cards which complete the former and the purpose of which is to make good the errors or insufficiencies of spelling. This type of index is very important, for in relations with foreign countries, the consonance of the name plays an important role in the writing of surnames. These index cards correspond to individual files, classified numerically and according to the year, which contain all the elements of information concerning wanted individuals or subjects of inquiries. Up to the present time about 60,000 cards have been put in the files since the reconstitution of the International Bureau; this figure has been doubled during the last two years;

(*c*) A ten-fingerprint file, which includes all the individuals reported to the ICPC, classified according to the Galton-Henry system. The latter is based on the seriation of fingerprints in four categories, according to the pattern;

(*d*) The single-fingerprint file, namely, a classification finger by finger. In principle this file only includes those malefactors guilty of very serious crimes. When a fragment of a papillary trace is found on the scene of a crime, a comparison is made between this fragment and the print in the file in which the card has only the imprint of one finger. The practical interest of this single-fingerprint comparison is to increase rapidity when searching in the files, by automatically eliminating those prints belonging to a category other than the one represented by the papillary trace to be identified;

(*e*) The archives of the International Bureau have also a file for photographs, inspired by the "speaking likeness system" by Bertillon and which deals with the peculiarities of the right profile of the face. Six parts of the latter have been taken as a basis: the fronto-nasal profile, the dorsal line of the nose, the inclination of the antitragus (part of the ear) in relation to the horizontal, orientation of the chin in relation to the vertical, inclination of the base of the nose, outline of the lobe of the right ear. The interest of this classification is to enable the discovery of the individual, concerning whom we possess only incomplete photographic elements;

(*f*) A file for specialists, where the individuals noted for their particular type of offences are classified. It specifies, as far as possible, the *modus operandi* of the malefactor, which sometimes enables us to discover him more easily or to warn the member States through circulars of the way certain gangs operate.

The International Bureau collects, in addition, the reproductions of objects of value of all kinds which are missing or have been stolen: jewels, paintings, works of art, rare documents, vehicles. They can be the subject of a general circulation in view of investigations.

It possesses also a small collection of counterfeit money, but as we shall see later on, the collection of legal and counterfeit money is in The Hague, in an office controlled by the ICPC.

With the object of assisting the development of the above-mentioned organization and to carry out the mission which it has undertaken, from preventive and primitive aspects of international crime, the International Bureau has set up a library which contains the principal penal law and scientific police reviews published by the member States and indicate the bibliographic sources with regard to criminology, criminalistics and police.

At the present time it receives about 150 reviews of all kinds. A selection of articles is made quarterly and sent to all the member States. A microfilm service enables us to give satisfaction to readers interested in any special article.

The ICPC has adopted four official languages: French, English, Spanish and German. It is for this reason that forms and surveys are written in these four languages; but the working languages are French and English, which are used for the circulations relative to malefactors and current correspondence.

B. THE NATIONAL CENTRAL BUREAUX

These offices extend to all countries the action of the International Criminal Police Commission through the intermediary of the International Bureau.

They constitute a sort of relay or first sorting centre, through the channels of which the activity of the international police radiates.

Their activity is orientated in three directions:

(*a*) In the direction of the International Bureau to which it communicates the information likely to be of use on the international plane;

(*b*) In the direction of the national central bureaux, when the activity of the international malefactor does not take place in more than two States, but even in this case, the International Bureau must be informed of the results of the investigations;

(*c*) In the direction of the criminal police authorities placed on the national territory.

In brief, it is a reception and forwarding information centre to be used or receive communications in the three above-mentioned directions.

The exchange also concerns inquiries where it is necessary to take action.

The national central bureaux are organized according to the norms which preside at the International Bureau, with general files, for specialities and fingerprints.

They also have powerful and rapid means of communication.

The exploitation is conceived according to the same methods but in a more restricted sphere.

Their role is not only punitive but preventive; they make all useful suggestions and point out the improvements which could be made in the fields of criminology, criminalistics and technical police, and maintain a permanent contact with the personalities capable of documenting them and thus make complete contribution in the struggle against crime.

It is owing to their joint efforts, together with the intense activities of all the services in these different domains, that the mechanism of the international police ensures total efficiency with regard to the task it has undertaken.

C. THE COUNTERFEITS AND FORGERIES DEPARTMENT

Owing to the development of counterfeiting and forging of currency credit instruments and official documents, the former Counterfeits and Forgeries Office in The Hague has also been reconstituted; the service is now located in this town and functions within the framework of the ICPC and under the control of the latter.

This centralizing service consists of two sections: on the one hand, it gathers specimens of legal paper currency, metal coins, instruments of credit; on the other hand, it collects counterfeit passports and identity cards and specimens of counterfeits of all sorts; these two categories of documents are transmitted to it by the member States, as soon as the official issue takes place or at the time of the discovery of the counterfeit.

It publishes the characteristics of the counterfeits and falsification by means of descriptions set forth as scientifically as possible.

The documentation received through the channels of the General Secretariat of the ICPC where the judicial exploitation is carried out in the first place, is published in the *Counterfeits and Forgeries Review* in Holland, which completes in this respect the *International Criminal Police Review*, concerning which we shall have a word to say later. Placed under the auspices of the ICPC but administered by the Dutch Government, this service interests not only the police world but also issuing agencies and important credit establishments, who are thus advised concerning recent counterfeits and forgeries.

A subscription service enables these agencies and establishments to obtain up-to-date information as soon as a forgery has been reported.

This documentation is supplied by the national central bureaux, with regard both to legal documents and counterfeit documents.

The delegated office in The Hague works in close relation with the International Bureau in Paris, through which channel passes all the correspondence.

Every three months it publishes recapitulative tables on observations made relative to counterfeiting currency. It also publishes a review, the details of which we will give below. The different types of counterfeits and forgeries are carefully studied and later described and published in this organ.

More than eighty States and territories give their assistance by furnishing collections of legal coins, notes and other documents.

III. The Functioning and the Means of Action of the ICPC

The various organizations examined would not be able to operate, and their efficiency diminished, if the institutions described did not have at their disposal powerful, perfected and rapid means of action.

In police work, scientific improvements and celerity are the two essential factors. The latter quality can easily be understood. Improved methods condition accuracy which is indispensable in matters of identification; information requires to be forwarded rapidly in order to achieve its purpose; the fidelity with which fingerprints are communicated depends on recent improvements in the methods of transmission. Any inexactitude in the terms or the images alters the truth and prevents identification.

Therefore, the ICPC has called upon experts in order to perfect the technique and the mechanism of its organizations.

The ICPC possesses two press organizations: The *International Criminal Police Review* and the *Counter-*

feits and Forgeries Review, which we have already mentioned.

It starts investigations and proceedings by means of perfected individual notices and uses, when necessary, an ultra-rapid system of communication.

(1) The *International Criminal Police Review* is published in French and English and appears ten times a year. It contains articles of doctrine on criminology, police, criminalistics and various monographs in connexion with these subjects, official communications and a recapitulative list of circulars concerning malefactors, which we will describe below. Professors, magistrates, doctors and police officials throughout the world contribute to this periodical. On account of the confidential information which it contains, it is for the use of these readers only.

A recapitulative list at the end enables a check to be made in order to see whether all the circulations have been received.

(2) The *Counterfeits and Forgeries Review* which is published in The Hague thanks to the financial and administrative assistance of the Dutch Government, is also published in both French and English.

It consists of the following sections:

Book 1: Counterfeits and forgeries: Section 1, Counterfeit notes and counterfeit coins; Section 2, Counterfeit cheques, securities and documents; Section 3, False passports; Section 4, Miscellaneous forgeries.

Book 2: Notes and coins in legal circulation: Section 1, Notes and coins in circulation; Section 2, Notes and coins withdrawn from circulation.

Its purpose is to furnish exclusively documentation concerning counterfeits. It interests not only police officials but also the issuing agencies and important credit establishments. Up to the present time about 500 subscriptions have been taken out by about forty countries.

This *Review* is produced in such a way as to make reference and manipulation easy and can easily be brought up-to-date by inserting the pages as they are published.

It supplies information about new currency issues, and gives the technical description of counterfeits and all useful indications for discovering forgeries.

(3) The *Circular* is a notice which on the international plane starts investigations.

On this point, the International Bureau has improved on the descriptive notices issued by the former Bureau which existed in Vienna (Austria) previous to 1939. The *Circular* was made, at that time, by separate documents which contained respectively the elements of identity: photos and fingerprints; thus there was the possibility of them getting lost. Certain of these elements were sometimes an integral part of the official organ, *International Public Safety*, a periodical which was published before the present *Review*.

At the present time all the elements of identification appear on the same form and are quite apart from the official organ. The separate individual notice is unquestionably better than the insertion in the *Official Bulletin*, its manipulation is easier and the *Circular* does not depend on the publication of the *Bulletin;* it is therefore a quicker method.

Thus the descriptive notice mentions, apart from the usual elements of identification (civil status, photos, fingerprints), the offence committed, the authority requesting search and, where necessary, a request for extradition.

In order to enable the different police departments to see at first glance the seriousness of the case to be dealt with these notices have, in the right upper corner, a special colour of which the signification is the following:

Blue mark: request for information and investigations for various reasons;

Green mark: the attention of the services to whom it is destined is drawn to the case of the identified malefactor whose movements should be watched.

Red mark: the malefactor should be sought and arrested by virtue of a warrant of arrest for trial or judgment.

Black mark: the notice concerns a body to be identified or a missing person.

Other notices show the photos of valuable articles which have been stolen and give a description of same. These are chiefly jewels, paintings and works of art.

Sometimes the International Bureau circulates notices in order to make known the criminal methods of certain individuals. The *modus operandi* of the latter is thus unmasked and all the police services to whom it is destined are warned against their activities.

(4) Radio communications

The International Bureau uses the usual methods for communicating information of all kinds: ordinary mail or air mail, telegraph and telephone.

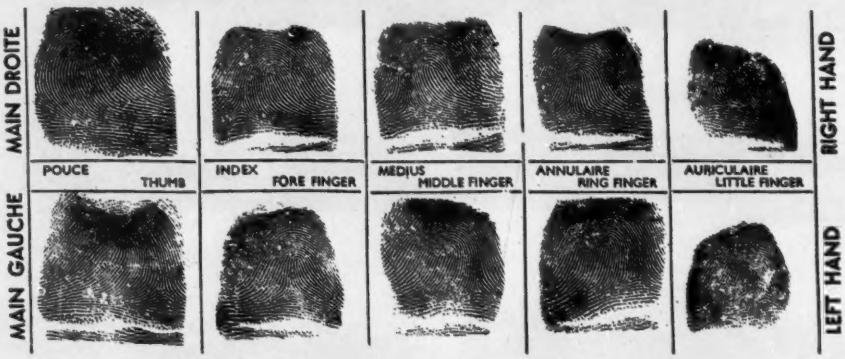
In cases of extreme urgency, the international radiocommunications network is employed. For this purpose the French Government has put at the disposal of the International Bureau three transmitters, one of 4 kW, which are located at the Paris Station. The network offers possibilities which are more than sufficient for present

CONFIDENTIAL

Y

Section : NARCOTICS

Born on August 15th 1913 in TINGHAU (China)
Nationality : Chinese
IDENTITY IS NOT CERTAIN.
Description : height 5 ft 7, black hair.
Previous convictions .
CURACAO (Dutch Indies) August 2nd.1950 a fine of 1000 gilders or 6 months imprisonment for drug trafficking (opium).



Miscellaneous information :
He was arrested on July 9th 1950 in CURACAO for trafficking opium (1880 grammes) probably coming from ROTTERDAM (The Netherlands). The individual in question is a sailor on board the Dutch tanker "SERONIA".

Reason for this circulation :
INTERNATIONAL TRAFFICKER TO BE WATCHED CLOSELY (ASSOCIATES-CHANGES OF ABODE) BY THE POLICE AUTHORITIES, THE CUSTOMS' AND THOSE AGENCIES WHICH ARE MORE PARTICULARLY ENTRUSTED WITH THE STRUGGLE AGAINST THE ILLICIT TRAFFIC IN NARCOTICS. In order to check his changes of abode, please inform the I.C.P.C., General Secretariat, 60 Bd. Gouvion St. Cyr, PARIS (INTERPOL PARIS) of any movements of this individual into or out of your Country.

I.C.P.C. PARIS
September 1950.

N° 571 a/50

T

Section : NARCOTICS

Born June 3rd 1905 at Douar de BOUANDAS in the district of OUED MARA (Constantine).

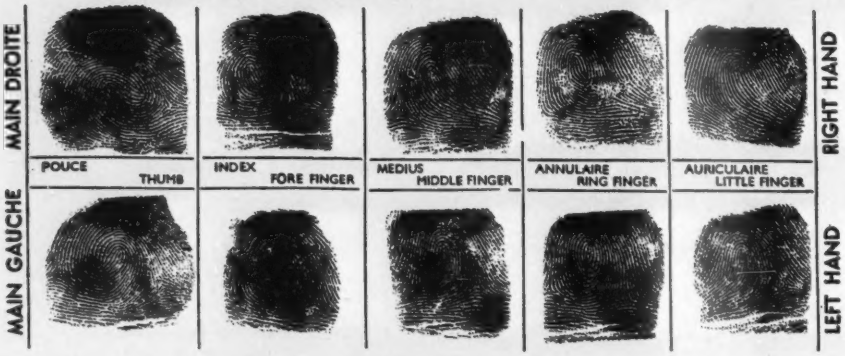
son of

Nationality : French of Algerian origin.

IDENTITY HAS BEEN CHECKED AND IS EXACT.

Description : height 5 ft.7 1/2, brown eyes, black hair going grey. Mole on the left side of the nose, scar about 1/3 of an inch on the right cheek bone, scar 4/5 of an inch long under the left jugular furrow underneath the ear.

Previous convictions : France (SAINT MALO) February 7th 1947, 10 months'imprisonment for trafficking false petrol coupons; Belgium (LIEGE) January 19th 1950 6 months'imprisonment for drug trafficking (14 tablets of 250 gr. and 20 tablets of 385 gr. of Indian Hemp.



Miscellaneous information :

According to the statements of the person concerned this drug was bought by him at ALGIERS. The tablets were in a cardboard package bearing the words "24/5 - PACKAGES-HARVARD-CHOCOLATE-COVERED-NUTCRUNCH".

Reason for this circulation :

INTERNATIONAL TRAFFICKER TO BE WATCHED CLOSELY AND DISCREETLY (ASSOCIATES - CHANGES OF ABODE) BY THE POLICE AUTHORITIES, THE CUSTOMS' AND THOSE AGENCIES WHICH ARE MORE PARTICULARLY ENTRUSTED WITH THE STRUGGLE AGAINST THE ILLICIT TRAFFIC IN NARCOTICS. In order to check his changes of abode, please inform the I.C.P.C., General Secretariat 11 rue des Saussaies PARIS (INTERPOL PARIS) of any movements of this individual into or out of your country.

I.C.P.C. PARIS
May 1950.

N° 175/50

needs and which will be adapted to new tasks according to the development of the stations to be connected.

The liaison between the centre and the International Bureau is made by teleprinter.

The transmitting centre in Paris is at the present time in constant liaison with the following stations: Bratislava Prague, Brussels, Copenhagen, Lisbon, London, Rome, Stockholm, Utrecht, Washington and Zurich.

The system for transmitting fingerprints or images by telegraph or radio has only been envisaged. Although experiments prove this method to be satisfactory, it would be necessary to generalize everywhere the technical installations which are very expensive.

Moreover, their utilization might lead to errors or imperfections, owing to atmospherics which could interfere in the circuit and blur the pattern.

The cost of this installation would seem, at the present time, out of proportion with the frequency of the cases envisaged.

For the time being, images of all kinds are sent by air mail.

IV. The ICPC and Preventive Arrest

We mentioned above that the practice of extradition was the most recent form of mutual assistance between the States, from the aspect of repression, before the institution of international police organizations.

But the practice of extradition has two inconveniences:

Before the procedure can be started, it is necessary to know the place of refuge of the criminal.

Moreover, once the place is known, the formalities of this procedure are very often long and the international malefactor, aware of the action concerning him, can change his domicile in order to hinder the action.

As we know, the procedure implies a transmission of documents through diplomatic channels and judicial authorities, and it must be recognized that the extradition treaties are no longer suitable for the necessities of the period.

The ICPC has endeavoured to remedy these inconveniences. Not because it wanted to by-pass the diplomatic or judicial authorities, for to consult the latter remains the normal procedure, but the police departments of the different countries can contact each other, in order to seek the international malefactor, before starting the normal procedure of extradition.

Then, on the basis of the procedure of provisional arrest which is provided for in the majority of extradition conventions as an urgent method, the police authorities in the place where discovery is made, take safety measures with regard to the individual wanted, and the goods which might be in his possession. This is the phase of preventive arrest.

During this lapse of time, which should be short, twenty-four or forty-eight hours, according to the country, the applicant public prosecutor's department is notified and immediately contacts the prosecutor's department in the State applied to and sends them a telegraphic demand for provisional arrest, in conformity with the texts in force.

From this moment a further period elapses during which the normal procedure of extradition takes its course. It is in this period that the documents concerning the case envisaged are transmitted and the matter is examined, after which comes the decision to extradite or not to extradite.

But the police have accomplished their task by putting the wanted individual at the disposal of the judicial authorities.

It is easy to understand that in international police matters celerity conditions the efficaciousness of the action, and by-passing momentarily the intermediaries of the normal procedure enables the International Bureau to arrest the guilty person in the shortest possible time, which might not have been done in other circumstances.

This arrest can take place either at sight of the international circular, described above, which contains all the elements of information desirable, or by telegram or radiogram, later confirmed by the judicial authorities of the requesting country and implying, in addition, the request for extradition.

V. The ICPC and the Campaign against the Illicit Drug Traffic

Our organization therefore takes action against crimes in ordinary law, but from the first it applied itself to combat the misuse of drugs, which, for two principal reasons, is an important branch of criminality.

First of all, owing to the relationship between the abuse of drugs and criminality; secondly, because it is a typical international offence, of which the consequences are felt beyond the frontiers of States.

The reports afterwards drawn up by the members of the ICPC and their work prove to the hilt the interest that the latter took in this problem.

For, whilst pointing out the danger, the ICPC created services and made practical arrangements in order to ensure the repression of the drug traffic.

Let us retrace the successive stages of its work in this field:

In September 1926, our Congress was held in Berlin and adopted a resolution demanding, besides an ap-

propriate legislation and the infliction of severe punishment, the setting up of a central service in each country, entrusted with the exchange of the names of drug traffickers and with all the documentation relative thereto.[4]

In 1928, following the fourth session of the ICPC in Amsterdam, the competence of the Direction of the Federal Police in Vienna, where the International Bureau was situated, was widened and two years later, at the Congress of Antwerp (Belgium), the creation of an International Bureau for dealing with drugs was particularly recommended as well as the organization of national central bureaux for the same purpose.[5]

Parallel with this work co-operation was established between our Commission and the League of Nations which had recognized the contribution of the police services, in the terms of a resolution which stipulated that "only specialized services could enable the Governments to discover and close down the clandestine drug factories and combat efficaciously the illicit traffic."[6]

It is for this reason that a delegation of members of the ICPC was appointed as technical experts to assist the diplomatic representatives at the sessions of the Advisory Committee on Traffic in Opium.[7]

Thus it took part in the Conference convened by the League of Nations and which ended on 13 July 1931, after having discussed the text of the international Convention for the limitation of the manufacture of narcotic drugs. The delegates of the ICPC drew up a draft Convention which was approved by the Advisory Committee on Traffic in Opium and amended by various governments, then again entrusted to the Committee of Experts, of which the ICPC was a member.[8]

The draft which resulted formed the basis of deliberations for the International Conference held in June 1936 and resulted in the final text of the Convention on the suppression of the illicit traffic in dangerous drugs.[9]

This international instrument was an event of the greatest importance, for it not only unified penal law but also confirmed the official institution of national central offices, on the model of those set up for counterfeit currency.

At the end of the Second World War, during which the international traffic was slowed down owing to the lack of transport and the hindrances put in the way of the free circulation of persons, the ICPC took up again the examination of this serious problem, foreseeing that when international communications came back to normal there would be a recrudescence of the traffic and that the conditions of war would increase the number of drug addicts because of the lawful use of medicaments with a narcotic basis in military establishments. The forecasts were not long before they became facts, the sources of supply were opened again, the currents of traffic were traced once more and a recrudescence was seen in international traffic.[10]

Therefore this question was put on the agenda of our general assemblies in Prague (1948) and Berne (1949).

The reports submitted during these two conferences aimed at two objects: putting at the disposal of the specialized services all documentation likely to orientate the investigations and establishing a practical and efficient system of surveillance and control.

With regard to the system, it is specified in the two resolutions which terminated the first of these assemblies and which aimed at a series of measures likely to intensify repressive action:[11] the specialization of the personnel, reconstitution of the appropriate services, increased and closer direct liaison with the International Bureau in Paris. It has, in addition, created a subcommittee entrusted with constantly following the question. The various measures are always being perfected.

In practice, the International Bureau has drawn up forms for cases of theft and traffic of drugs in order to increase the efficaciousness of repression. They were drawn up in a similar way to those of reports of information requested of the different governments by the Commission on Narcotic Drugs. The communication of these particulars does not duplicate the reports of seizures addressed by the governments to the Secretariat of the United Nations, but, in this way, we wish to ensure harmony and to combine useful efforts towards repression.

In the reports submitted to the general assemblies of the ICPC in Prague and in Berne, we already endeavoured, in this same spirit and in order to reach the same objective, to set side by side the documentation gathered by the United Nations and that obtained by the International Bureau itself.

In order to co-ordinate the work of the repressive services on the international plane, the general secretariat periodically circulates recapitulative tables of cases brought to its notice. These tables published for information purposes do not take the place of direct interventions which continue to emanate from the International Bureau in Paris in each particular case.

Harmonizing its efforts with the action of the United Nations in this field, the ICPC drew the attention of its members to the new danger which appeared under the form of synthetic drugs, but on this point, the repressive action of police authorities depends on the drawing up of legislative measures and international agreements which will place certain drugs not specified by the conventions under international control.

The ICPC, as also the Commission on Narcotic Drugs, noticed that aircraft were used more and more by traffickers; therefore our organization decided to cen-

tralize the cases of illicit traffic by air, at the International Bureau.

Thus, a resolution adopted at the General Assembly of Berne recommended the reporting of all offences or traffic occurring by means of commercial or tourist planes, and to make known, through the distribution of confidential memoranda, the planes and members of crews suspected of repeated illegal trafficking on an international scale.[12]

Knowing the particular situation of the illicit traffic existing in Occupied Germany and resulting from the existence of enormous stocks of drugs abandoned by the German army, the secretariat general of the ICPC convened a conference which was held in Paris, on 22 and 23 February 1949, and at which were present the representatives of the three Inter-Allied Zones in Western Germany and the representatives of the frontier countries, with a view to promoting closer co-operation in matters of criminal police, in particular in the fields of drugs and counterfeit currency.

The definitive political status of this part of Germany being in evolution, transitory dispositions were adopted during this meeting in order to ensure as efficiently as possible the repression of the drug traffic, and, under cover of the Allied Occupation Authorities, close relations were established with the German authorities in criminal matters.

This initiative should be placed side by side with the recommendation adopted by the Commission on Narcotic Drugs and addressed to the Occupation Authorities tending towards unification of the control of drugs in Germany.[13]

Moreover, a regional conference of the principal countries of Western Europe, concerned with the struggle against the illicit traffic of drugs, took place in Geneva on 22 and 23 September 1950. Ten countries were present and two United Nations delegates attended as observers.

In order to establish this co-operation on a truly practical and efficient basis, the executive committee of the ICPC wishing to take advantage of the privilege which is attached to its consultative status, decided to entrust to the writer of this article the task of representing this organization at the fifth session of the Commission on Narcotic Drugs which was held at the United Nations from 1 to 16 December 1950.

After having described, before this specialized institution, the general principles which regulate our Commission, we endeavoured to show in concrete terms, the methods of this co-operation.

There were two questions on the agenda of the fifth session which concerned more particularly the ICPC: the illicit traffic and the unification of the international conventions on drugs. Concerning these two questions, which both tend towards the efficacy of repression, there must be constant liaison between the Division of Narcotic Drugs and the general secretariat of the ICPC.

It is for this reason that the ICPC should be mentioned in article 28 of the draft of the Single Convention which provides for close collaboration between the secretariat of the Commission on Narcotic Drugs on the one hand and on the other certain public international organizations interested in the control of drugs.

The ICPC can be called upon to express its opinion in the same way as it is called upon to give its opinion at the Commission on Social Questions concerning the following subjects: white-slave traffic, counterfeiting currency, juvenile delinquency, prevention of crime and the treatment of delinquents.

But, above all, one must be persuaded that the ICPC is an active organization entrusted on the international plane with the search and pursuit of criminals in all parts of the world. Therefore, it wishes to offer its assistance to the United Nations, not only by giving it technical advice on social questions relative to criminality, but by putting into action all the repressive services of its organization.

It does not duplicate with the Commission on Narcotic Drugs, for it has no initiative in the field of legislation and regulations; it is still less a rival organization of the Commission on Narcotic Drugs and can but complete the action of the latter on the repressive plane.

The ICPC must therefore be considered as a complementary organization, an auxiliary of the Commission on Narcotic Drugs, and its action should be in conformity with the struggle organized by this specialized institution and in complete agreement with it.

The ICPC would be willing to execute certain tasks of a police nature which might be entrusted to an international organization in charge of the control of illicit traffic on the plane of judicial investigations. It would, indeed, be in a position to carry out this mission, of course, in liaison with the Division of Narcotic Drugs.

This activity appears to me to represent a particularly useful form of co-operation in this field.

A precedent of this co-operation between the United Nations and the ICPC exists in matters of counterfeit currency. Indeed, following the Convention of Geneva on counterfeiting currency adopted on 20 April 1929, the Conference adopted the following recommendation:

"IX—that pending the creation of an International Office as referred to in Art. 15 of the Convention, the work of the International Bureau at Vienna[14] which was fully appreciated by the Conference should be continued with the completest possible co-operation of the Governments, according to the information supplied to the Conference, the International Bureau by centralizing information as to counterfeiting currency, displays an

activity which is directed to the task which might be allotted to the organization contemplated in Article 15".[15]

As delegate to the Commission on Narcotic Drugs, we suggest that this body recognize in a resolution this privilege of co-operation and beg to submit for consideration that the International Criminal Police Commission has an advantage over an international organization solely concerned with the question of drugs, owing to the fact that it occupies itself with international criminality in general, so that from this aspect, it is in a position to uncover cases of drug trafficking which may come to light, principally or secondarily in examining other cases of crime.

Recognizing the utility which our organization may offer, the Commission on Narcotic Drugs in its session of 5 December 1950, submitted to the Economic and Social Council the following decision:

"The Commission decided to record its appreciation of the offer of co-operation extended by the International Criminal Police Commission which, considering the relations already established between that Organization and the Economic and Social Council, it will be happy to accept as likely to contribute to the achievement of the aim of the Commission on Narcotic Drugs to suppress the illicit traffic in dangerous drugs."[16]

* * *

The advisability of this co-operation once accepted, let us show with some typical examples the results obtained through the co-ordination of national police forces, under the direction of the International Bureau.

1st example: Case Sch ... Ts ... L ...

On 10 September 1948, a Chinaman named Sch . . . Ts . . . L. was arrested in Boston (USA) for being in possession of 15 pounds of opium. A letter found on him was transmitted to the International Bureau.

This note had been sent by a compatriot W... G... L... domiciled in Amsterdam.

At the request of the International Bureau, the Dutch police carried out investigations in Amsterdam which resulted in a certain quantity of opium being seized at the domicile of W... G... L...

2nd example: Case C... François.

In January 1949 in New York, the US Customs seized on board ss "Bastia". 20 kgs. of opium and 5 kgs. of heroin.

The inquiry established the fact that the drugs had been imported into America by a certain C. . . member of the crew of the "Bastia". C... succeeded in escaping and is still wanted by the US authorities.

The International Bureau was notified that C... François had been identified as being C... François, born on 28 January 1896, in Forbo Ocagnano (Corsica), having been convicted in France twice for drug trafficking.

C... was arrested on September 1950 in Dunkirk for white-slave trafficking as he was taking a woman on board a ship leaving for Saïgon where she was to lead a life of prostitution.

C... will shortly be questioned in the prison in Marseilles, where he has been transferred, on his activities in the United States.

3rd example: The case of S. . . Michel.

In September 1949, the Canadian police arrested in Montreal, for trafficking in important quantities of heroin, an individual calling himself S... Michel, born on 18 January 1908, in British Columbia.

The Canadian authorities, doubting the exactitude of this civil status, transmitted to the International Bureau certain information which had been found in the notebook seized on the individual.

The fingerprints of the self-styled S... were also sent to the International Bureau.

Investigations made by the International Bureau with the collaboration of the French police, permitted the establishing of the fact that the so-called S... was in reality d'A... Antoine, called M., born on 18 December 1914, in Bone (Algeria), convicted five times in France and Algeria, for theft, aggravated theft and treason.

The inquiry also proved that d'A... was called in 1945, in Paris, F... Louis.

An examination of the records of the International Bureau resulted in a file being found in the name of an individual called F... Louis, called M... claiming that he was born on 19 November 1914, in Bone.

On 15 April 1948, in San Remo (Italy), this person had helped to manufacture counterfeit foreign currency.

The photograph found in the file of E... Louis proved beyond question that d'A... and F... Louis were one and the same person.

Unfortunately, the so-called S. . . Michel having been provisionally released in Canada, did not answer the summons of the judicial authorities, when the information furnished by the International Bureau was received.

He is now a fugitive who is being sought actively.

The police and justice services in Canada, Morocco, Algeria, Italy and France, will know, henceforward, the exact situation as regards this person.

There are numerous similar examples. But we have sufficiently shown by what means the ICPC accomplishes its high mission of social protection throughout the world, and can thus be placed among the most active and efficient international institutions.

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[1] Mr. DONNEDIEU DE VABRES, "Les principes modernes du droit pénal international" (Modern principles of international penal law).

[2] Mr. DONNEDIEU DE VABRES, "Les principes modernes du droit pénal international" (Introduction. Modern principles of international penal law).

[3] Mr. LOUWAGE, President of the ICPC — Speech pronounced at the General Assembly of the Belgian Union of Penal Law in Brussels.

[4] International co-operation in the judicial police field (Memorandum of the ICPC, Vienna, 1928, chap. X).

[5] See Report No. 5 by Dr. Bruno SCHULTZ, September 1931, 8th session.

[6] League of Nations document: OC. 1581, page 10.

[7] Before the Second World War, a specialized sub-committee on the repression of the illicit traffic composed of police officials met at regular intervals some time before the Advisory Committee on Traffic in Opium.

[8] See Doc. C. 455 M. 193 — 1931 XI., Geneva, 26 August 1931, pages 31 and 32.

[9] Refer to Report by Dr. Bruno SCHULTZ, No. 3, 13th session of the ICPC 1937; for the text, see *International Public Safety* dated 31 October 1936.

[10] See Mr. MARABUTO's Reports No. 5 and 8, "The struggle against the illicit traffic of drugs"— No. 8, Prague Conference (September 1948) and Berne (October 1949).

[11] See the *International Criminal Police Review*, No. 21, October 1948, page 19, and No. 33, December 1943, pages 24 and 25.

[12] The *International Criminal Police Review*, No. 33, December 1949, page 18.

[13] See documents E/CN.7/206 dated 21 November 1950 and E/CN.7/217 dated December 1950.

[14] At that time, the head office of the ICPC.

[15] Doc. C. 153.M.59—1929 II—Geneva, 1 May 1929, page 22.

[16] Doc. E/CN.7/216, dated 29 December 1950.

Narcotic Drugs and Penal Law

By Arnulfo Martínez Lavalle, Licenciado,

Alternate Delegate of Mexico to the Commission on Narcotic Drugs

1. Human criminality is an individual and group phenomenon which has afflicted society from the earliest days. The exact form it takes will depend on the stage of the community's cultural evolution. A civilization may even be said to create forms of illegal conduct corresponding to its own degree of development. Crime adapts itself to the age, and in that sense is relative. It violates the cultural values protected by the law, but the form and characteristics of the violation are invariably dictated by the social conditions under which it takes place.

2. The illicit traffic in narcotic drugs clearly illustrates this point. Narcotics have, of course, been known from ancient times; but the advance of chemistry and the discovery of synthetic drugs have opened up a vast new field of action which has given all countries cause for perpetual concern. The various systems of law throughout the world have been compelled to provide for these newest forms of crime, and a great many sections have been devoted to them in criminal law and penal codes.

3. According to modern concepts of criminal law the only weapon against crime, apart from the elimination of social factors which may give rise to criminal conduct or moral degeneration, is punishment, which under a system of safeguards can take place only after an offence has been committed. Consequently the creation of offences, essentially a legislative task, is of paramount importance in the fight against crime. The aim of criminal policy, as part of penal theory, is to frame the law as best to prevent, try and punish crime and deter and avert repetition. This is one of the most important functions of government, for its purpose is to prevent rupture of social bonds and change in the social order.

4. Offences connected with the use of narcotic drugs have necessarily been classified according to the particular forms they take. Legislators have had to survey the various types of criminal activity and to analyse the offenders' *modus operandi*. The classification arrived at is given below.

A. Traffic

5. One form of criminal activity in this field is illicit traffic in narcotic drugs, by which is meant clandestine trade carried on outside the control of the health authorities. It has of course been necessary to classify the drugs which require such control because they are habit-forming and harmful. In Mexican law, as in almost all the world's legal systems, this subject is dealt with in the public health code, as is only natural, since medicine, not law, indicates which raw or manufactured substances possess harmful qualities. On that classification the legislator bases the scope of the penal law and decides when clandestine trade in such substances shall be considered a criminal offence not only because it is punishable as a breach of administrative regulations, but also because it suggests, and indeed—I emphasize—proves, the existence of activities injurious both to the individual and to mankind.

6. While various forms of traffic should generally be regarded as a material activity conditioned by modern transportation facilities, traffic should be clearly understood to mean the circulation of substances which, because of their harmful qualities, are classed as narcotic drugs subject to administrative control. In short, traffic means any trade in manufactured narcotics or in raw material or seeds from which alkaloids or narcotic drugs may be derived.

7. Because of the new modes of transportation in use today, illicit traffic presents an acute problem for criminal policy; consequently legislators tend to assess the various forms of this criminal activity in relation to the method of transport used, and to regard as traffic not only the actual trading but also the transportation which makes it possible. A new and important form of this crime is international traffic, which has called for the enactment of severe penalties. The Mexican Penal Code, for example, imposes heavier penalties for international traffic and for the production and manufacture of narcotics intended for import. It does so because of the need for the collaboration of all countries in the international prevention of the illicit traffic in narcotic drugs. Narcotic drugs are often produced and manufactured not for illicit consumption at home but for export to, and use in, other countries. Hence it should be noted that illicit traffic in narcotics provides a vast field of action for

criminal policy, which, when it deals with crime connected with narcotic drugs, in effect becomes an international criminal policy.

8. It should also be noted that while all systems of law contain general provisions with regard to smuggling, they place narcotic drugs in a special category and punish more severely any attempt, whether successful or unsuccessful, at international traffic in those commodities. This fact is of great importance, since crime connected with narcotic drugs is usually the work of international gangs, which exploit the shortage in some countries of narcotics and of the means of producing and manufacturing them.

B. Production and Manufacture

9. If we define production simply as the process of obtaining opium, Indian hemp, coca leaf, or other substances, which may serve as raw materials for the chemical preparation of narcotic drugs, the proper criminal policy is to prevent them from being obtained illegally. They must of course be produced to satisfy medical and scientific needs, but such production should be strictly controlled and clandestine production severely punished. At present a highly commendable effort is being made, with the support of all the States signatory to the international conventions in this field and with the aid of the United Nations, to establish a world control of production of basic substances for medical and scientific needs only.

10. Legislatures have been obliged to make the clandestine production of basic substances and procurement of raw materials a criminal offence in order to control the total production and to cut off supplies to the illicit market.

11. Manufacture has so many features in common with production that when it is clandestine it too should be regarded as a crime and the operation of clandestine laboratories should entail condign punishment. The prevention of clandestine manufacture has a number of special aspects: control of lawfully operating laboratories; general investigation of the activities of professional and amateur chemists; and observation of the level of normal stocks required by each country for its medical and scientific needs.

12. These functions should be entrusted to both administrative and police authorities, so that the former may, apart from any penal action, revoke licences issued for the exercise of professions more or less closely connected with those functions. Administrative regulations should be based on statute and should be consistent with and likely to promote a criminal policy aimed at preventing illicit traffic in and clandestine production and manufacture of narcotic drugs.

C. Administrative Control

13. Health authorities too should endeavour by regulations to prevent illicit traffic from utilizing legal channels. Such regulations should lay down the conditions under which physicians and pharmacists may dispense medicines containing narcotic drugs; the forms in which narcotic drugs may be prescribed for treatment; the provision that all medical prescriptions for narcotic drugs should be written on special numbered forms issued by the health authorities and that licences may be revoked administratively for prescribing narcotics on unofficial forms, without prejudice to prosecution in suitable cases; specification of the maximum quantity of a narcotic drug which may be prescribed as part of a chemical compound for the treatment of various diseases with regard to its effect and periodic use as required by the treatment; conditions under which properly-authorized establishments, such as pharmacies and chemical laboratories, may purchase and sell narcotic drugs, to be dispensed on medical prescription, subject to periodic visits by health inspectors; strict prohibition of the sale of narcotic drugs not compounded in the proportions permitted by regulation, in order to prevent their use by addicts even on medical prescription, except for gradual disintoxication treatment in properly-supervised private or public institutions.

14. Administrative control should include the general regulation of imports of basic substances and manufactured narcotic drugs by means of import certificates. These certificates should be issued by the health authorities with due regard to the stock requirements previously declared by them and in accordance with the restrictions which the various international conventions impose on signatory and recommend to the attention of non-signatory States.

15. These measures represent the elementary requirements of a proper criminal policy in this field; they should by no means be regarded as exhaustive.

16. Close international co-operation is vitally necessary if the campaign against illicit traffic and the clandestine production and manufacture of narcotic drugs is to be successful. In view of the different constitutional systems of the various countries, identical legislation for this problem is out of the question; hence international conventions must be concluded, laying down a minimum series of measures to reduce the illicit use of narcotic drugs and establishing systems of information exchange, control and penalties to be enacted for violation. Study of the new forms of criminal activity connected with the clandestine use of narcotic drugs and the need for imposing severe penalties on all such acts have led to the creation of new criminal offences in domestic systems of law. Thus certain new provisions have been introduced into the Mexican Penal Code dealing exhaustively with all criminal activities involving the use of narcotic drugs.

On theoretical grounds and for the sake of better classification, these criminal activities have been grouped under the general heading of "Offences against the public health". Such a classification makes it possible to regard as offences a wide range of activities, irrespective of the means of their performance, and encompasses all forms of crime which in any way injure health by the specific use of narcotic drugs. Consequently traffic, trade, possession, manufacture, purchase, transfer, gift and any act related to the acquisition or supply of or traffic in, seeds or plants having the character of narcotic drugs, are punishable; and any act amounting to general instigation, or the act of illicitly inciting, inducing or assisting another person to use narcotic drugs or seeds or plants of the same character, are likewise criminal offences. This provision, which results from a recent reform of the Penal Code, establishes a new type of offence known as "proselitism with regard to narcotic drugs". This provision covers two basic aspects: instigating the use of narcotic drugs, i.e., inducing a person to begin or continue the use of narcotics; and procuring the commission of acts connected with the production and manufacture of narcotic drugs. This provision of the Mexican Penal Code completes the full series of offences against the public health constituted by the handling of narcotic drugs or by related acts.

17. In accordance with the latest developments in penal law, the Mexican Penal Code does not itself give a scientific definition or a classification of narcotic drugs, but considers that these matters are technically and scientifically within the scope of the Public Health Code, the body of law defining and classifying narcotic drugs. Consequently the Penal Code regards as narcotic drugs those designated as such in the Public Health Code and in the international conventions which Mexico has signed or may sign in the future. Mexican criminal legislation on the matter thus obeys the precepts of penal theory in merely making an act a criminal offence when it forms part of the traffic in narcotic drugs. It is worth noting how Mexican criminal law regards and attempts to solve these problems in its provisions based on international conventions. In our times traffic in narcotic drugs, like traffic in persons and similar criminal activities, is part of the subject matter of an emerging international criminal law. It may therefore be said that Mexico's criminal policy embraces all possible kinds of illegal activity in regard to narcotic drugs. In pursuance of that policy, Mexico is a member of the United Nations Commission on Narcotic Drugs; it has signed all the relevant international conventions and scrupulously carries out all the resulting obligations.

18. Although criminal policy is regarded as a science subsidiary to penal jurisprudence, its usefulness, development and value in the teaching of law have been clearly demonstrated by the German criminologist Franz von Liszt in a number of learned studies and treatises. I regard it as a most important branch of penal jurisprudence because it helps to translate theory into practice and thus represents the teleological aspect of penal law —the determination and attainment of the ends for which penal law is established.

19. Scrutiny of the problem of criminal acts connected with narcotic drugs is an essential part of their prevention, and the whole world is now concerned with its solution. Hence the work of the United Nations Commission on Narcotic Drugs and of the Division of Narcotic Drugs is especially valuable, for they base it on high regard for the health of all mankind, and endeavour to direct an appropriate criminal policy against the use of narcotic drugs which injure and debase man. They are thereby carrying out the fundamental purposes of the United Nations Charter by promoting a better development of the various countries which constitute the world and which in the final analysis have but a single nationality: the human race.

20. Our present stage of cultural development obliges all nations to fight shoulder to shoulder against crime, and especially against crime connected with narcotic drugs, which is clearly becoming international. The nations of the world will recognize thereby that they are bound to depend on each other if they are to satisfy their common needs, since they are all parts of the same whole: humanity.

Study of experimental habituation to morphine*

By Denise G. Fichtenberg

The Bulletin *hereafter presents the first part of an original work, fruit of many years' research and experiments on the very controversial question of habituation to morphine. The author, a Doctor of Natural Sciences, is chief of biological work at the Laboratory of Physiological Control of Anti-venereal Medicaments (French Ministry of Public Health), and has achieved experimentally the state of habituation in the rat, has worked out techniques of biological assay for morphine, studied the fixation of morphine in the organism and its elimination, and discovered that the organism of habituated animals transforms or destroys more morphine than that of normal animals.*

Introduction

It has long been known that the human organism can tolerate usually toxic doses of certain poisons without grave consequences, provided those doses are administered regularly. This acquired tolerance has been given the name of mithridatism or habituation.

In a man who takes morphine daily, the symptoms are characteristic and complex.

As a result of repeated administration of the drug, the usual doses cease to have their elective effect upon many individuals. To cause analgesia, increasingly larger doses, even in excess of normally toxic quantities, have to be used. This principal phenomenon is in most cases accompanied by an overwhelming craving for the drug, and the withholding of the latter causes phenomena known as disorders of abstinence or deprivation.

Since the phenomena of deprivation or abstinence characteristic in the morphine addict are not normally found in morphinized animals or with the majority of poisons giving rise to habituation, a number of authors (Jeanne Levy, 1934; R. Cahen, 1935) distinguish, at least for the purpose of experimental study of the mechanisms of habituation, between habituation proper and abstinence phenomena.

Nevertheless, in the case of morphine, a theory of the mechanism of habituation to this substance has to explain both the weakening of analgesic action and the tolerance of toxic doses which are characteristic of habituation proper, as well as the craving for the drug.

The state of habituation has aroused the curiosity of many experimenters who have tried in vain to discover more about its mechanism. They have worked along different lines and followed different conceptions; their results are often contradictory. No valid explanation of habituation has been found so far.

Much work has been done to determine by comparative methods what becomes of morphine in the organisms of normal and habituated animals and how it is eliminated. So far, however, no proof has been adduced of more rapid or more complete disappearance of morphine in the case of habituated animals. It should be noted that the divergencies observed by various authors can be explained: (1) by the lack of precision with which the degree of habituation in tested animals has been determined in most cases; (2) by the difficulty of extracting, describing and assaying morphine in tissues, biological liquids and excretions.

In this study I have tried to verify two theories advanced in the past, namely that: (1) morphine becomes transformed into its oxydation product, oxydimorphine; (2) morphine circulates in the blood in a less concentrated form in the organisms of habituated animals than in those of normal animals.

Before undertaking a study of what happens to morphine in the organism of animals, I had to resolve two fundamental problems: (1) that of finding an animal showing habituation phenomena, upon which a series of experiments could be carried out; (2) that of establishing a specific and sufficiently precise method of assaying morphine, oxydimorphine and morphine accompanied by oxydimorphine.

* The Bibliography of the article will be found at the end of the second part in the next issue of the *Bulletin*.

Having at my disposal an animal capable of habituation—the rat—and a pharmacological test permitting the detection of 0.030 mg. of morphine accompanied by oxydimorphine, I worked out a simple method of extracting morphine from tissues and biological liquids, and studied the fixation of morphine and its conjugated form in various organs and its elimination. The purpose of this work was to measure the quantity of morphine administered and determine what percentage of morphine is converted within the organism into a substance devoid of analgesic effect.

The following plan was used in preparing the study:

FIRST CHAPTER. EXPERIMENTAL ESTABLISHMENT OF THE STATE OF HABITUATION

Part one: Critical review of previous studies

I Animals used.
II Tests employed to control the state of habituation.
III Summary and criticism.

Part two: Selection of an animal capable of morphine habituation

I Effect of repeated morphine injections upon mice.
II Habituation of rats:
(A) Tolerance of toxic doses of morphine hydrochloride;
(B) Physical condition of rats habituated to morphine;
(C) Diminution of analgesic action during habituation;
(D) De-habituation;
(E) Reaction to hypnotics of rats habituated to morphine;
(F) Habituation to heroin;
(G) Summary.

SECOND CHAPTER. BIOLOGICAL ASSAYS OF MORPHINE

I Catatony of the mouse's tail.
II Action of cholinic esters on the denervated muscle of the leech under the influence of morphine:
(A) Study of the sensitizing action of morphine on the acetylcholinic contraction of the denervated muscle of the leech;
Establishment of a biological assay of morphine;
(B) Study of the antagonist effect of morphine on the contraction caused by various cholinic esters in the denervated muscle of the leech;
Establishment of a biological assay of morphine and oxydimorphine.

THIRD CHAPTER. WHAT HAPPENS TO MORPHINE IN THE ORGANISM

Part one: Detection of oxydimorphine

I Action of blood on morphine *in vitro.*
II Detection of oxydimorphine *in vivo.*

Part two: Disappearance, conjugation and accumulation of morphine in vitro *by tissues and* in vivo *in normal and habituated rats*

I Action of certain tissues upon morphine.
II Content of free and conjugated morphine in the blood and tissues of normal and habituated rats.

Part three: Elimination of morphine

I Elimination of free and conjugated morphine through the urine and faeces of normal rats.
II Elimination of free and conjugated morphine through the urine and faeces of various groups of habituated rats.

Part four: Comparison between quantities of morphine accumulated in the organism or eliminated by normal and habituated rats

CONCLUSIONS

First chapter

Experimental Establishment of the State of Habituation

In the first part of this chapter I shall relate briefly and critically the work of various experimenters who have tried to build up tolerance experimentally,* then in the second part I shall describe my personal research.

PART ONE

CRITICAL REVIEW OF PREVIOUS STUDIES

After reviewing the various animals which were experimented upon, I shall examine the various tests used by those conducting the experiments to establish the degree of habituation of animals subjected to morphine.

I. Animals used

The animals most frequently used are the dog,[1] the rabbit[2] and the rat.[3]

The literature on the subject also contains accounts of a considerable number of experiments per-

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* In a very complete survey Eddy has studied tolerance and habituation in all animal species.

[1] Faust (1905); Van Egmond (1911); Myers (1916-1939); Takayanaki (1934); Tatum, Seevers and Collins (1927, 1929); Pierce and Plant (1927, 1930, 1932); Barbour, Hunter and Richey (1929); Hotta (1932); Birk (1933); Giordano (1933); Koh (1933); Schmidt and Livingston (1933); Wolff, Riegel and Fry (1933); Cahen (1934-1935); Hayashi (1934); Ikeshima (1934); Anton and Birk (1935); Plant and Slaughter (1936-1938); Donnini (1937); Gross, Plant and Thompson (1938); Wada, Tanaka, Hirano and Taneiti (1936); Barbour, Porter and Seelye (1939); Gross and Thompson (1940); Thompson and Gross (1941); Gross (1942); Slaughter, Treadwell and Gales (1943); Wright and Sabine (1943); de Bodo (1944); Goetz, Burril and Ivry (1944); Shideman (1946); Templetõn, Calapeaux and Adler (1940); etc.

[2] Cloetta (1903); Marie (1907); Van Egmond (1911); Takayanaki (1924); Gottlieb (1926); Tatum, Seevers and Collins (1929); Sue (1932); Koh (1933); Cahen (1934, 1935, 1936); Hayashi (1934); Ro (1934); Ko (1935); Shou (1935); Keil and Pohls (1936); Donnini (1937); Puru (1937); Hinohara (1937); Kuwahara (1937-1938); Delaville (1938); Emerson and Phatak (1938); Endo (1938); Ingersoll (1940); Okawa (1940); Sato (1940); Tin (1940); Yosikawa (1940); Ra (1940); Wright and Sabine (1943); etc.

[3] Rubsamen (1908); Hildebrandt (1922); Takayanaki (1924); Joel and Ettinger (1926); Ma (1932, 1933, 1936, 1937, 1939); Cheng and Ma (1934); Hayashi (1934); Cross and Pierce (1935); Himmelsbach, Gerlach and Stanton (1935); Weger and Amsler (1936); Amsler (1937); Donnini (1937); Fitshugh (1939); Seevers and Shideman (1941); Dietrich and Thienes (1941); Shideman and Seevers (1941, 1942); Lewis (1949); etc.

formed on the guinea-pig,[4] the mouse,[5] and in more exceptional cases the cat[6] and the monkey.[7]

In these animals habituation was realized through the injection of morphine over varying periods (several days, several months, several years) by various methods (intramuscular, subcutaneous, intraperitoneal, buccal); the morphine is administered either in small constant doses (Gross and Thompson, 1940; Goetz, Burril and Ivry, 1944, with dogs), or in progressively increasing doses (Ma, 1932, with rats) or in rather large doses from the outset (Schmidt and Livingston, 1933, with dogs; Rubsamen, 1908, with rats).

II. Tests employed to control the state of habituation

To control the degree of habituation of animals experimented upon, the authors resorted to one or more of the four following tests:

(1) Diminution of the analgesic effect produced by the active initial dose.

(2) Tolerance to toxic doses for normal animals.

(3) Disappearance of secondary actions brought on by morphine.

(4) Particular reaction of animals habituated to morphine to the active initial dose of various substances (cross habituation).

On the basis of the definition of habituation given in the introduction, the first two tests used simultaneously may be considered as characteristic of that state provided they are applied to a sufficient number of animals. On the other hand the application of the other two tests to animals habituated to morphine has not been studied sufficiently systematically to make it possible to determine the degree of habituation of animals on the basis of these two tests alone.

Many authors have not experimented systematically and simultaneously with the first two tests which are characteristic of habituation and have merely verified the weakening of the analgesic action or the various secondary effects of morphine.

To give only a few examples, we may mention Rubsamen (1908) who notes the tolerance of the rat to morphine as soon as he can absorb food, half an hour after the injection; Himmelsbach, Gerlach and Stanton (1935), who evaluate the degree of habituation of the rat by his greater or lesser irritability when he is placed in an abnormal position after the injection; Kobayashi (1930), who observed a diminution in the narcotic effect and in myosis in the dog and rabbit while the rhythm of the heart, respiratory frequency and vagal action are not modified; Tatum, Seevers and Collins (1929), who observed in dogs habituated to morphine a weakening in the analgesic and vomitive action, a greater tolerance of heroin, codeine, chloralhydrate and barbiturates without any simultaneous material variation in the minimum lethal dose.

The divergent and sometimes contradictory observations hitherto noted are no doubt due to this lack of homogeneity and precision.

We shall examine below the results obtained by using these various tests.

(1) Reduction of the analgesic effect produced by the active initial dose

Few authors have systematically studied the wearing off of the analgesic effect brought about by the regular administration of morphine. Nevertheless it has been shown by a variety of tests that in dogs, tolerance to analgesia is not established, while that tolerance is manifest in guinea-pigs and rats.

Goetz, Burril and Ivry (1944), who gave daily subcutaneous injections of 3 mg. of sulphate of morphine per kg. to *dogs* for fifty days, measured the threshold of painful excitement produced on the dental pulp by electric stimulation. The thresholds of painful sensations were measured twice a week, firstly before the injection of morphine and secondly thirty, sixty and ninety minutes after the injection. The threshold of pain after rising, decreases following the daily injections, only to increase again with the effect tending to vary periodically. The authors conclude that during the period of daily administration of a uniform dose of morphine, the analgesic action decreases but the tolerance is not lasting and disappears and re-appears periodically.

Weger and Amsler (1936) determined in the normal *guinea-pig*, and every two days during the daily administration of morphine, the number of stimuli required to produce a squeal after subcutaneous injection of 50 mg. of morphine hydrochloride. The analgesic action decreased in the course of the experiments.

Rentz and Kesarbani (1941) made subcutaneous injections of increasing doses of morphine hydrochloride, varying from 25 to 100 mg. per kg. from sixty to eighty days on *guinea-pigs*. As from the twenty-first day the animal was no longer sensitive to the painful sensation observed with the active initial dose in the normal guinea-pig.

Lewis (1949), using the Ercoli and Lewis test (1945) (reaction to thermic stimulus) in *rats*, measured the degree of analgesia caused by morphine, heroin, codeine, dilaudide and demerol (dolosal). In particular in a group of twenty rats which received subcutaneous daily

[4] Amsler (1931); Fleischman (1931); Keeser, Oelkers and Raetz (1933); Hayashi (1934); Bertschik (1934); Weger and Amsler (1936); Donnini (1937); Matschulan (1937); Delaville and Russel (1938); Rentz and Kesarbani (1941); Frommel, Piquet, Cuehod, Loufti and Aron (1945).

[5] Kreitmair (1928); Keeser, Oelkers and Raetz (1933); Koh (1933); Hayashi (1934); Cahen (1935); Favarget and Rosselet (1944).

[6] Cold (1929); Tatum, Seevers and Collins (1929); Hotta (1931); Hayashi (1934).

[7] Tatum, Seevers and Collins (1929); Abe (1936); Hotta (1931); Seevers (1934); Yokota (1935).

injections of 10 mg. of sulphate of morphine per kg. for six weeks, the analgesic effect decreased regularly until it reached 40 per cent of its original force.

(2) Tolerance to toxic doses for normal animals

To establish this tolerance, the minimum lethal dose must be determined accurately. The majority of the research workers who have studied the mechanics of habituation have failed to determine it with sufficient precision. Nevertheless, experiments made on various animal species show on the one hand that in the dog, the guinea-pig, the rabbit and the mouse, there is no tolerance to doses which would be toxic for normal animals, whereas a certain tolerance is built up in the rat. Thus Rubsamen (1908) and Hildebrandt (1922) were able to make subcutaneous injections in the last-mentioned animal of doses between 710 mg. per kg. and 1,000 mg. per kg., doses which are known to be much higher than the toxic dose for the normal animal.

Dog:

Tatum, Seevers and Collins (1929), experimenting on twenty dogs, indicated that the toxic dose varies from 200 to 416 mg. per kg. for normal animals and from 250 to 416 mg. per kg. for animals having received subcutaneously 3 mg. per kg. of sulphate of morphine daily for six months. Schmidt and Livingston (1933) observed the development of tolerance to a dose of 100 mg. per kg. in one month in dogs which received 30 to 60 mg. per kg. daily, three-and-a-half to four months in dogs receiving 2 to 10 mg. per kg. daily. The mortality rate was much higher in the first case than in the second.

Cahen (1935) did not work on a sufficiently large number of animals to enable him to determine the habituation of the dog to morphine. He injected dogs subcutaneously every two days for two-and-a-half to three months with progressively increasing doses from 1 to 35 mg. per kg. and obtained the results indicated in the table given below:

Determination of the minimum lethal dose for normal and habituated dogs (according to Cahen, 1935)

	Normal dog		Habituated dog	
Dose of Mo. (HCl) in mg/kg.	No. of animals experimented on	No. of deaths	No. of animals experimented on	No. of deaths
100	2	0	2	0
135	5	5	4	1
150	2	1	5	2
200	–	–	2	1

Templeton, Calapeaux and Adler (1940) merely observed that a dose of 162 mg. of sulphate of morphine injected intravenously produces the same rate of mortality in normal dogs and those habituated to morphine.

Rabbit:

Experiments made on rabbits are not any more precise. It should be noted indeed that toxicity in rabbits varies considerably with age, according to Eddy (1939) who experimented on 3,000 young rabbits. The difference of toxicity according to age may explain the contradictory results obtained by the different authors referred to.

Tatum, Seevers and Collins (1929) found that after prolonged administration of morphine, this animal cannot bear a minimum lethal dose greater than the dose tolerated by the normal adult animal, 100 to 200 mg. per kg.

Cahen (1935), who administered morphine hydrochloride to rabbits for three months by subcutaneous injection, in increasing doses varying from 1 to 50 mg. per kg. notes that a dose of 200 mg. per kg. injected intravenously causes the death of five out of six rabbits while the ratio is four out of six in normal animals.

On the other hand, Furu (1937) pointed out that the rabbit tolerates large doses of morphine after repeated injections of heroin and codeine. It is probably a matter of cross-habituation.

Guinea-pig:

Cahen (1935) experimented with guinea-pigs after regular administration of morphine. Every two days, the animals received subcutaneous injections of morphine hydrochloride in doses varying from 0.4 to 200 mg. per kg. The toxicity created subcutaneously had the following results:

Determination of the minimum lethal dose for normal and habituated guinea-pigs (according to Cahen, 1935)

	Normal animal		Habituated animal	
Dose in mg/kg.	No. of animals	No. of deaths	No. of animals	No. of deaths
500	7	3	–	–
550	6	6	7	5

Rat:

The experiments made with rats were not conducted with sufficient attention to detail especially as Cheu and Robbins (1944), studying the toxicity of sulphate of morphine injected intravenously, found that young rats were more sensitive than older animals, and the age of the animals is not mentioned in the experiments made by Rubsamen (1908) and Hildebrandt (1922). Moreover, Rubsamen did not systematically determine the minimum lethal dose for normal animals and animals habituated to morphine. He merely noted that 510 to 600 mg. per kg. of morphine hydrochloride injected subcutaneously was toxic for the normal animal. By administering 300 mg. per kg. to a group of rats, he obtained a mortality of about 50 per cent. He injected doses increasing gradually up to 710 mg. per kg. in the survivors and observed a reduction in mortality. Hildebrandt (1922) habituated young rats during their period of growth to subcutaneous injections of morphine. The doses are increased slowly from 100 to 600 and 1,000 mg. per kg.

Mouse:

Cahen (1935) injected increasing doses of morphine hydrochloride from 10 to 60 mg. per kg. into mice sub-

cutaneously daily for two-and-a-half months and obtained the following results:

Determination of the minimum lethal dose for normal and habituated mice (according to Cahen, 1935)

	Normal animals		Habituated animals	
Dose in mg/kg.	No. of animals injected	No. of deaths	No. of animals injected	No. of deaths
620	6	3	–	–
650	6	6	6	2

The mouse habituated to morphine thus tolerates a dose only slightly larger than that tolerated by the normal animal.

(3) Disappearance of the secondary effects of morphine

Many research workers have assumed that an animal becomes accustomed to morphine when there is a change in the various secondary effects of the drug: sedative action, action on thermogenesis, action on respiration, on the cardiac vagus, on the pupil, on vomiting, on the gastro-intestinal tract and on the genital organs.

The observations of the various authors do not always concord. The over-all results obtained show that the variations in the secondary effects of morphine in the habituated animal are not simultaneous: the sedative action is the first to disappear, the cardiac vagus becoming habituated later. The divergences noted in connexion with the secondary effects may arise from the method of habituation and from the species of animal subjected to experiment, as will be seen from the description which follows:

(a) *Narcotic and sedative action.* A normal animal injected with morphine falls into a drowsy state for a varying length of time. Repeated doses of the drug reduce the length of the period or eliminate it. The authors observed that the state of drowsiness is characterized particularly by a change in posture reflexes or reflexes of the lower limbs, and the animal's irritability after the injection. They noted that the monkey, dog, rat and mouse withstand the sedative effect of morphine.

In the monkey: Hotta (1931) and Seevers (1934) observed a weakening of the narcotic effect of morphine beginning on the third day of regular injection of the drug.

In the dog: Plant and Pierce (1927) note only a reduction in the duration of the state of drowsiness as the animal becomes accustomed to the drug.

Tatum, Seevers and Collins (1929), by regularly injecting 3 mg. per kg. in the animal obtain no more than a slow weakening of the state of drowsiness. On the other hand, Kobayashi (1930) reports that a dose of 60 mg. puts a normal dog to sleep while 2 g. in the same animal once he is habituated leaves him awake after the injection.

Wilker and Frank (1948) show that in the spinal dog the reflexes causing the flexing and extending of the hind leg become weaker after a single dose of morphine and return to normal with regular injections of the drug.

According to Kobayashi (1930) the *guinea-pig* does not become accustomed to the sedative effects of morphine.

Himmelsbach, Gerlach and Stanton (1935) noted irritability in the *rat* when tied to a board and flagellated. In its normal state, this animal becomes insensible after an injection of morphine. After eight days of daily injections of morphine, the animal struggles under the influence of the initial dose.

Cahen (1935) notes slight drowsiness in the normal *mouse* which precedes catatony of the tail; in the mouse habituated to morphine, he observes only the catatonic state without drowsiness.

(b) *Action on thermogenesis.* Morphine lowers the temperature of the normal animal. This action has been studied during habituation in the *rabbit;* the results obtained are contradictory.

While Girndt and Lipchitz (1931) find no habituation to thermal morphine reactions by chronic intoxication of the animal, Cahen (1935) notes a rise to more than one degree above normal in the temperature of the rabbit habituated to morphine for three months, and Ko (1937) points out that the hypothermy induced by morphine in the normal animal disappears with repeated injections of the drug.

(c) *Action on respiration.* In the normal animal, morphine has a depressive effect on respiration which takes the form of a great diminution in the frequency and an increase in the depth of respiratory movements.

The disappearance of the respiratory action due to morphine, after repeated and prolonged administration of the drug, has not been noted in all cases in different animals, nor by all authors in the same animal.

In *monkeys* Hotta (1931) states that a few daily injections of morphine eliminate the cyanosis engendered by a single injection of morphine in a normal animal.

In *dogs* habituated to morphine, Van Dongen (1915), Schmidt and Livingston (1929), Hotta (1931) and Cahen (1935) report the disappearance of the inhibitory effect of morphine on the respiration; on the other hand, Tatum, Seevers and Collins (1929) noted no distinct changes in the respiratory response after prolonged administration, for four months, of 3 mg. per kg.; these results are definitely confirmed by Kobayashi (1930), who reports the same slowing down of respiratory frequency after injections of morphine in normal dogs and dogs habituated to the drug.

Hotta (1931) reports that in *cats* no habituation of the respiratory centre was observed after forty-three daily injections of morphine into those animals.

Cahen (1935) and Okawa (1940) observed that the depressive action of morphine on the respiratory system of the *rabbit* did not change throughout the prolonged administration of the drug.

(d) *Action on the cardiac vagus.* Morphine gives rise to bradycardia in normal animals by stimulating the vagal centre. This stimulation, principally observed in dogs, does not change in animals habituated to morphine, according to Tatum, Seevers and Collins (1929) and Kobayashi (1930), or is diminished slightly, according to Hotta (1931), by the regular administration of morphine for twenty to twenty-two months.

(e) *Pupillary reaction.* An injection of morphine gives rise to myotic action in *monkeys, dogs* and *rabbits.* Hotta (1931) noted that myosis in these animals disappeared on the repeated administration of morphine. The same phenomenon had already been reported by Van Dongen (1915) and Kobayashi (1930) in dogs.

In normal *cats,* morphine brings about mydriasis, which persists after prolonged administration of the drug (Hotta, 1931).

(f) *Vomitory action.* The generally acknowledged emetic effect of morphine on normal dogs is questioned by Tatum, Seevers and Collins (1929) and Cahen (1935), who state that a large dose of morphine administered immediately has no emetic effect on a normal animal.

The vomitory action of the drug is said to be less in dogs habituated to morphine (Van Dongen, 1915; Downs and Eddy, 1928; Tatum, Seevers and Collins. 1929; Cahen, 1935), and in cats (Hotta, 1931). Nevertheless, according to Hotta (1931), this action persists in dogs habituated to morphine.

(g) *Gastro-intestinal phenomena.* (∝) *In situ.* In normal animals, morphine gives rise to a decrease in the tonicity, frequency and extent of stomachic movements, to an increase in the tonicity and peristaltic movements of the small intestine and of the ileo-caecal sphincter and to an increase in the tonicity of the rectum.

The effect of morphine on the gastro-intestinal tract is not greatly changed by the repeated administration of the drug. Van Egmond (1911) showed that the depressive action of morphine on the stomach persists in dogs habituated to morphine. Miller and Plant (1926) and Templeton, Calapeaux and Adler (1940) found that daily injections of morphine into dogs continued to produce a marked increase in the tonicity, extent and frequency of intestinal peristaltic movements. On the other hand, Cahen (1935) observed a decrease in the intestinal effects of morphine on dogs habituated to morphine.

A morphine injection usually produces a diarrhoeic effect on a dog. Kobayashi (1930) and Hotta (1931) found that this effect continued in an animal chronically under the influence of morphine; Du Mez (1919), Plant and Pierce (1928), Schmidt and Livingston (1929), and Tatum, Seevers and Collins (1929), observed a decrease in defaecation and a tendency to constipation in animals habituated to morphine.

(β) *Isolated organ.* The tonicity of the isolated intestine of a normal animal is reduced when it is placed in contact with a solution of morphine. The phenomenon is reversed in the case of the isolated intestinal loop of an animal which has received morphine regularly. This effect was observed by Kobayashi (1930) in the isolated intestines of the dog and rabbit and by Jeanne Levy and Cahen (1933) in the isolated intestines of the rabbit and guinea-pig.

(h) *Action on the genital organs.* (∝) *Development of the genital organs.* The regular administration of morphine prevents the normal development of the male or female genital organs, as was observed by San Fillipo (1939) in young dogs which had received the drug regularly for twelve months. The genital organs suffered fatty degeneration and the ovaries contained no mature follicles. Morphinism in mice disturbs the genital cycle (Ko, 1939).

(β) *Isolated organ.* Morphine causes increased tonicity if it is placed in contact with the isolated uterus of a normal rabbit. Kobayashi (1930) observed the contrary reaction of the uterus to morphine in a rabbit which received daily injections of the drug; Ko (1939) observed only a decrease in tonicity.

(4) Special behaviour of animals habituated to morphine on receiving the active initial dose of various substances (cross-habituation)

Research workers have thought it interesting to study the action of depressive or stimulating poisons on animals habituated to morphine and to base the proof of habituation to morphine on these findings.

Jeanne Levy (1934) has made a very complete summary of these studies and I shall only quote the most recent ones, which are confined to opium derivatives, phenanthrenic alkaloids, cocaine, apomorphine and hyperthermics. There has been no recent research on the effect of barbiturates on animals habituated to morphine.

(a) *Opium derivatives and phenanthrenic alkaloids.* Rabbits habituated to morphine can tolerate doses of opium alkaloids, phenanthrenic alkaloids or their mixtures: pantopon, laudanum, narcophine, dilaudide, dicodide, and heroin, which are usually fatal to normal animals (Keil and Poels, 1936). The hyperglycemic effect on these animals of heroin, codeine, dionine and pantopon is also less (Ko, 1935).

(b) *Cocaine.* The local analgesic effect of cocaine on the cornea of a rabbit is increased, both in intensity and duration, after a preliminary injection of morphine. Bertschik (1934) and Amsler (1935) observed a reversal of this phenomenon in rabbits habituated to morphine; cocaine no longer acted as a local anesthetic.

(c) *Apomorphine.* The vomitory action of apomorphine is reduced in dogs habituated to morphine. Issekutz and Varady (1934) used this action as a test of the existence of habituation in dogs.

(d) *Hyperthermics.* Plant and Slaughter (1936) found that the buccal administration of 5 mg. per kg. of dinitrophenol (a hyperthermic with peripheral action) in a bicarbonate solution, which gives rise to heightened metabolism in normal dogs, had no effect on animals habituated to morphine. This result was confirmed in rabbits by Cahen (1935), who also found that hyperthermics with central and peripheral action (brewers' yeast, tetrahydronaphthylamine) give rise to greater hyperthermy in animals chronically intoxicated with morphine.

III. *Summary and criticisms*

Dogs, rabbits, guinea-pigs, rats and mice are the animals most generally used for the study of experimental habituation to morphine. Their behaviour during the prolonged administration of the drug has given rise to varying or contradictory comments.

The authors have not ascertained with sufficient care the existence of habituation in any given animal. They observed differences in the behaviour of the functions and organs of animals which received the drug regularly.

The most typical phenomena of habituation to morphine, tolerance of doses which would be toxic to a normal animal and the lessening or disappearance of the analgesic effects of morphine, have not been experimented on systematically and the results obtained have not been confirmed by all research workers. A toxic dose may be determined by different methods. At present, there is a tendency to determine the dose which is lethal in 50 per cent of cases; this can have no meaning, however, unless the experiment is conducted on a sufficient number of animals of the same species, sex and weight, uniformly fed throughout the experiment and kept at a uniform temperature.

The analgesic effects of morphine can be determined by means of different tests on the same animal; but in all cases the experiment should be carried out under absolutely identical conditions on normal animals and on animals receiving morphine regularly.

The results obtained by various research workers, who have not always operated under the above conditions, lead to the following conclusions:

(1) In *dogs*, habituation to analgesic effects is not manifest; although the toxicity has not been determined accurately, this animal does not tolerate doses greater than those which are toxic to normal animals. The habituation of dogs to morphine was assumed when the secondary effects of the drug were found to have disappeared, each experimenter studying a few specific symptoms. These secondary effects did not all disappear at the same time: the sedative effects diminished first, whereas the vagal action continued for a long time and the effect of morphine on intestinal movements was unchanged. It therefore seems difficult to define the degree of habituation of a dog, which is very small and differs greatly from that observed in human beings.

(2) *Rabbits.* After regular administration of morphine, they cannot tolerate doses which are toxic for normal animals. Most of the secondary effects of morphine remain in animals which are chronically intoxicated. Rabbits cannot therefore be used for the experimental study of habituation.

(3) *Guinea-pigs.* The doses tolerated by them are only slightly greater than those which are generally toxic for a normal animal; here again, experiments in toxicity are extremely incomplete; the analgesic effects of morphine diminish during the period of daily administration, but the secondary effects of morphine remain. The guinea-pig is not, therefore, the most suitable animal.

(4) *Rats.* According to Rubsamen (1908) and Hildebrandt (1922), they tolerate approximately three times the 50 per cent lethal dose for normal animals and, unlike other research workers, the above authors administered these large doses to animals for considerable periods; nevertheless, neither the disappearance of analgesic effects,[8] nor the changes in the secondary effects of morphine have been studied systematically and concurrently.

(5) *Mice.* In spite of certain somewhat unconvincing experiments, these animals were used by Cahen (1935) in experiments in connexion with the study of habituation.

PART TWO

Selection of an Animal Capable of Morphine Habituation

Having at my disposal a selected stock of mice and rats, I carried out experiments on these two species of animals.

I found that the two main tests, the simultaneous application of which makes it possible to demonstrate with accuracy an animal's habituation to morphine, were the following:

(1) Tolerance to doses which would be lethal for a normal animal;

[8] Lewis (1949) made a comparative study of the analgesic action of morphine and of certain synthetic analgesic substances.

(2) Diminution or disappearance of the analgesic effects caused by the administration of the active initial dose of morphine; reappearance of those effects with the administration of larger doses.

Tolerance to lethal doses can easily be demonstrated by the determination of doses 50 per cent lethal before and after repeated administration of the drug. It is, however, very important to take into account the method by which the poison is introduced into the organism. When administered by intravenous injection, morphine reaches the organs much more quickly than when administered by subcutaneous or intramuscular injection, and may on that account undergo less complete transformation in the blood and muscles. If that were so, a habituated animal would only be able to tolerate by intravenous injection a dose slightly larger than that tolerated by a normal animal, whereas it would tolerate a much larger dose administered by subcutaneous injection.

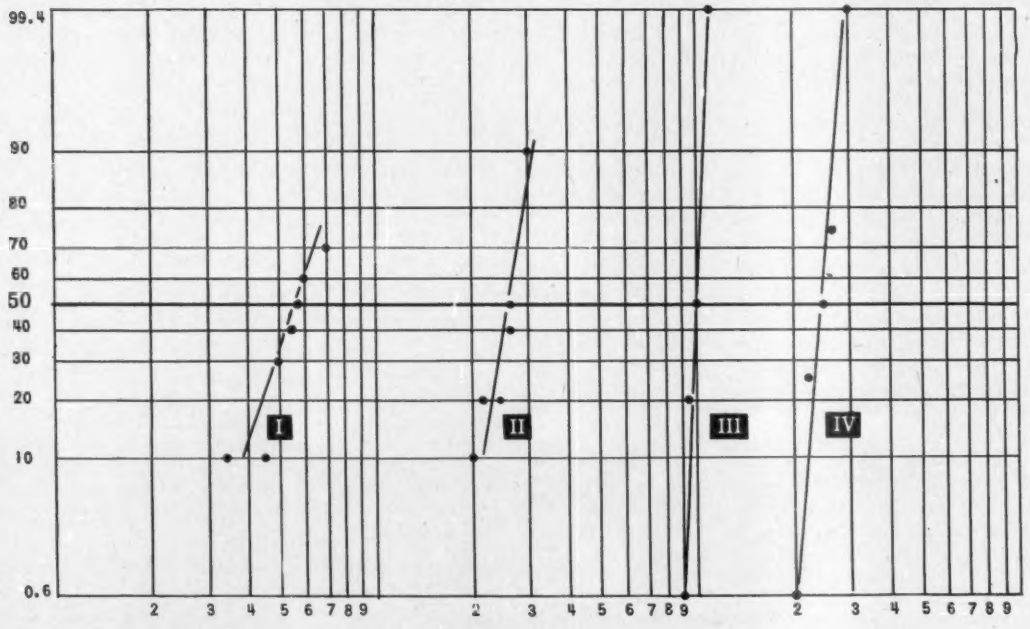
Moreover, Jeanne Lévy (1945) has stressed the significance of the ratio toxicity by subcutaneous injection/toxicity by intravenous injection. This is generally about 3(2.5 to 3.5) for poisons which are eliminated unchanged or which only undergo slow transformation in the organism. It may reach higher figures for poisons which are rapidly transformed in the organism into substances less toxic than themselves, while it is less than 2 for poisons which are rapidly transformed into substances more toxic than themselves. The value of this ratio might have led to the discovery of data on the changes undergone by a substance in the organism, and I made a systematic study of it.

Furthermore, since according to some authors morphine is liable to be transformed *in vivo* into oxydimorphine, I also determined the toxicities of that substance in the normal animal when administered by subcutaneous and intravenous injection.

My first research was carried out on the mouse. Since that animal showed no tolerance to 50 per cent lethal doses of morphine administered by subcutaneous or intravenous injection after daily treatment for two months, I gave up the mouse and turned to the rat which, when habituated to morphine for a certain length of time, has a definite tolerance to doses which would be lethal for the normal animal. I carried out a number of experiments on the rat which made it possible to establish the degree of habituation to morphine. I studied in succession the attenuation of the analgesic action of morphine in the course of habituation, and the behaviour of a habituated rat to hypnotics (evipan, soneryl). Finally, I studied the rat's habituation to another analgesic, heroin.

I. *Effect of Repeated Morphine Injections upon Mice*

The first experiments were carried out on the mouse (D. Fichtenberg, 1946) in order to verify whether that



Toxicity curves

animal showed a certain degree of tolerance to morphine during the regular administration of the drug. The animals used, which were about five weeks old and whose growth had been regular, weighed 16 to 19 g. at the beginning of the experiment.

(1) *Determination of the 50 per cent lethal dose of morphine hydrochloride when administered by subcutaneous and intravenous injection*

(a) *Subcutaneous injection.* Group of ten or twenty mice were given an injection of a 2 per cent solution of morphine hydrochloride in the flank. The animals, kept at a constant temperature (21°C.), were examined after twenty-four hours and the mortality percentage was noted.

Determination of the toxicity of morphine hydrochloride administered by subcutaneous injection

*Dose (δ per g.)**	*Number of animals*	*Mortality percentage*
350	10	10
450	10	10
500	10	30
550	20	40
580	20	50
600	10	60
700	20	70

To calculate the average individual variation for a 50 per cent lethal dose, the toxicity curve is plotted on Bonet-Maury logarithm-probability paper. The ordinates are the mortality percentages (projection of the S curve along a straight line), and the abscissae are the logarithms of the doses administered.

In the above example (Graph I on page 26) the different points obtained make it possible to draw a straight line which passes approximately through all the points.

The average variation for the 50 per cent lethal dose is calculated by applying the formula $E = \sqrt{\frac{s \times t}{n}}$ where

t is the mortality percentage
s the survival percentage
n the number of animals utilized

$$E = \sqrt{\frac{50 \times 50}{20}} = 11$$

When marked on the toxicity graph ± 11 corresponds to doses of 540 and 610 respectively. The 50 per cent lethal dose being 580, the difference is: —40 and +30, with a maximum of +40.

The percentage error is $\frac{40 \times 100}{580} = 6.9.$

The 50 per cent lethal dose of morphine hydrochloride when administered to the mouse by subcutaneous injection is 580 ± 40 δ per g.

(I) If ten animals are used instead of twenty:

$$E = \sqrt{\frac{50 \times 50}{10}} = 16.$$

* In this article, δ = microgram.

(b) *Intravenous injection.* Groups of ten or twenty mice were injected in a vein of the tail with a 2 per cent solution of morphine hydrochloride in physiological serum. They were kept at a temperature of 21°C. and examined after twenty-four hours and the percentage established.

Determination of the toxicity of morphine hydrochloride administered by intravenous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
200	10	10
225	10	20
250	20	40
260	20	50
300	20	90

Average variation for the 50 per cent lethal dose: II (Graph II, page 26).

50 per cent lethal dose: 260± 20 δ g.
Percentage of error: 7.6 per cent.

(c) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* For morphine hydrochloride this ratio is 2.2, which, according to Jeanne Lévy (1945), would appear to indicate that morphine is not transformed or undergoes very slow transformation in the mouse's organism.

(2) *Determination of the 50 per cent lethal dose of oxydimorphine hydrochloride administered to the mouse by subcutaneous and intravenous injection*

I used oxydimorphine hydrochloride prepared in the following way:

(a) *Preparation of oxydimorphine.* I used the Fulton (1933) method with some changes. 2.5 g. of morphine hydrochloride are dissolved in 50 c.c. of water. The base is precipitated with 5 c.c. of standard soda, and the alkalinity of the solution is checked after vigorous shaking. A 1 per cent solution of potassium ferricyanide is added gradually and the liquid is shaken up by electricity for one hour. The presence of an excess of ferricyanide is checked by persistence of the yellow colouring of the solution. The liquid is centrifugalized and decanted and the precipitate is washed twice with distilled water. The precipitate is dissolved over heat in N/5 hydrochloric acid. To obtain complete transformation of the morphine into oxydimorphine, it is preferable to filter and to repeat the same operations again on the filtrate. The final precipitate, dissolved in hydrochloric acid, is brought to a 6.5 pH by means of concentrated ammonia. It is centrifugalized and the decanted liquid is checked to see that it has a pH of 6.5, and that a few drops of dilute ammonia do not make the top liquid turn milky. The latter operation is repeated a second time to purify the oxydimorphine. The final precipitate is washed twice with warm distilled water, which dissolves the mineral salts, and then once with pure alcohol and once with ether. It is then dried in the oven at 37°C.

To check that the product obtained is free from any trace of morphine, Marquis's reagent is used. A small quantity of alkaloid is powdered on a watch glass with a small drop of 12 volume hydrogen peroxide. A drop of sulphuric acid with formalin added to the watch glass produces an emerald-green colouring characteristic of oxydimorphine, whereas traces of morphine give a violet tint spoiling the green coloration.

The base is transformed into hydrochloride by dissolving it in 0.2 N hydrochloric acid and it is evaporated over a water bath to obtain the hydrochloride in the dry state.

(b) *Toxicity by subcutaneous injection.* Groups of ten mice were injected in the flank with a 2 per cent solution of oxydimorphine hydrochloride. After twenty-four hours the following mortality percentages were obtained:

Determination of the toxicity of oxydimorphine hydrochloride administered to the mouse by subcutaneous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
200	10	0
500	10	0
700	10	0
1,000	10	0
1,500	10	35
2,000	10	65

Average variation for the 50 per cent dose: 16.
50 per cent lethal dose: 1,750 ± 10 δ per g.
Percentage of error: 0.57 per cent.

(c) *Toxicity by intravenous injection.* The mice, having been injected in a vein of the tail with a 2 per cent solution of oxydimorphine hydrochloride in physiological serum, were examined after twenty-four hours.

Determination of the toxicity of oxydimorphine hydrochloride administered to the mouse by intravenous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
50	10	0
60	10	0
70	10	0
80	10	100
90	10	100
100	10	100

Average variation for the 50 per cent lethal dose: 16.
50 per cent lethal dose when administered by intravenous injection: 75 ± 2.5 δ per g.
Percentage of error: 3.3 per cent.

(d) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* For oxydimorphine hydrochloride this ratio is 23.3. This substance is sharply differentiated from morphine by the 50 per cent lethal dose being very much greater when administered by subcutaneous injection and very much smaller when administered by intravenous injection. The high value of the ratio R indicates, according to Jeanne Levy (1945), that it must be rapidly transformed in the mouse's organism into a substance less toxic than itself.

(3) *Behaviour of mice subjected to daily injections of morphine hydrochloride*

The difference in the reaction of the mouse to morphine and to oxydimorphine is sufficient to determine whether the morphine is transformed more completely into oxydimorphine in habituated animals than in the normal animal.

I sought to habituate mice to morphine and determined in these animals the toxicity of this substance after subcutaneous and intravenous injections, as well as the ratio: toxicity by subcutaneous injection/toxicity by intravenous injection.

The mice were treated every second day for two months by means of subcutaneous injections of increasing doses of morphine hydrochloride. The injections are made into each flank alternately; the flanks are cleansed with a 60 per cent alcohol solution both before and after injection. The animals are kept at an even temperature (21°C.).

The morphine hydrochloride is dissolved in distilled water; the concentrations are determined on the basis of an injection of 0.50 c.c. of liquid for a mouse weighing 20 g.

The quantities injected are in proportion to the weight of the animals, which are weighed before injection. The initial dose is equal to 0.050 mg. per g. of body weight. During subsequent weeks the doses are increased from 0.025 mg. per g. twice a week to 0.275 mg. per g. at the beginning of the eighth week.

A total of 124 male mice were used in the experiment, the mortality rate being about 10 to 12 per cent per week. The catatony of the tail caused by morphine is the same at the beginning and at the end of the experiment, during which the physical aspect of the mice remains normal.

(4) *Determination of 50 per cent lethal doses of morphine hydrochloride*

Fifty-one mice survived after eight weeks. Toxicity in these animals is determined by the subcutaneous and intravenous injection.

(a) *Subcutaneous injection.* The mice are injected in the flank with 1 per cent solutions of morphine hydrochloride, and are examined twenty-four hours after the injection.

Determination of toxicity of morphine hydrochloride administered to mice habituated to morphine by subcutaneous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
550	10	0
600	10	60

The 50 per cent lethal dose of morphine hydrochloride administered by subcutaneous injection is about 0.590 mg. per g.

(b) *Intravenous injection.* A solution of 1 per cent morphine hydrochloride in physiological serum was in-

jected into a vein in the tail of the mice. They were examined twenty-four hours after the injection.

Determination of toxicity of morphine hydrochloride administered to mice habituated to morphine by intravenous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
200	5	0
250	10	100
300	8	100

The 50 per cent lethal dose of morphine hydrochloride administered by intravenous injection amounts to approximately 0.225 mg. per g.

(c) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* The 50 per cent lethal doses determined after regular injection with morphine hydrochloride are absolutely comparable with those determined in the normal animal.

The ratio of toxicities by these two methods is equal to 2.6, which is not far from that obtained in normal mice (2.2).

Morphine thus does not appear to undergo any speedy change in the organisms of mice subjected to repeated injections of the drug. The mice, after a period of two months, are unable to tolerate doses, whether subcutaneous or intravenous, in excess of the toxic dose for normal mice. Cahen (1935) noted, from experiments on a small number of mice, a very low rate of tolerance in habituated mice, the mortality rate of which was 34 per cent as against 100 per cent.

(5) *Summary*

As mice habituated to morphine show no tolerance of doses which are toxic for normal animals, they cannot be used in a study of the mechanism of habituation. I accordingly made no further experiments with this animal.

II. *Habituation of Rats*

As stated earlier, the authors who experimented with rats did not determine with sufficient precision the degree of habituation which may be attained by this animal.[9] Thanks to homogeneity, selective breeding and the large number of animals placed at my disposal, I was able to undertake a series of experiments to determine the degree of habituation of animals to which morphine had been administered daily by various methods.

A. *Tolerance of toxic doses of morphine hydrochloride*

This study, parallel to that undertaken with mice, consists in determining the toxicities of morphine and of oxydimorphine in the normal rat, according to the method of injection; and in the daily injection of increasing doses of morphine and the determination of the toxicities of morphine in rats habituated to the drug. (Fichtenberg, D. G., 1948). A study is also made of the speed of habituation of the rat subjected for a period of three days to twelve weeks to constant doses or to doses increased at more or less rapid rates.

The rats utilized, whether males or non-pregnant females, three months old, have a regular rate of growth and weigh at least 20 g. at one month, 40 g. at two months and 75 g. to 80 g. at three months.

(1) *Determination of the 50 per cent lethal dose of morphine hydrochloride administered to normal rats by subcutaneous or intravenous injection*

(a) *Subcutaneous injection.* The animals are injected in the flank with a 4 per cent solution of morphine hydrochloride. They are kept at an even temperature (21°C.) and examined after twenty-four hours. Preliminary toxicity tests are made on groups of four rats, and the 50 per cent lethal dose is determined on twenty rats (ten males and ten females). The results are as follows:

Determination of the toxicity of morphine hydrochloride administered to the rat by subcutaneous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
200	4	0
225	4	25
250	10 males	50
250	10 females	50
275	4	75
300	4	100

There is no difference in toxicity between males and females. Average variation for the 50 per cent lethal dose: 11 (Graph IV, page 26). 50 per cent lethal dose when administered by subcutaneous injection: 250±10 δ per g. Percentage of error: 4 per cent.

(b) *Intravenous injection.* Preliminary experiments were also undertaken on groups of four rats. A 2 per cent solution of morphine hydrochloride in physiological serum is injected into the internal saphena of a hind foot. The rats are examined after twenty-four hours.[10]

The following mortality rates were observed:

Determination of the toxicity of morphine hydrochloride administered to the rat by intravenous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
40	4	0
50	4	0
70	4	0
80	4	0
90	4	0
95	5	20
100	10 males	50
100	10 females	50
110	4	100

Average percentage for the 50 per cent lethal dose: 11. 50 per cent lethal dose of morphine hydrochloride

[9] As this chapter was in the course of preparation we received Lewis' article (1949) which determines with precision the development of tolerance in the rat to the analgesic effect of morphine.

[10] Animals injected by this method die within two to six hours. None were found to die beyond that period.

administered by intravenous injection, identical in males and females: 100 ± 3 δ per g.

Percentage of error: 3 per cent (Graph III page 26).

(c) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* The ratio for morphine hydrochloride is 2.5. It seems to show that morphine is converted very slowly in the organism of rats as in that of mice.

(2) *Determination of the 50 per cent lethal dose of oxydimorphine hydrochloride administered to rats by subcutaneous and intravenous injection*

Since hydrochloride is only slightly soluble in water, the quantities of oxydimorphine to be injected obliged me to prepare benzoic sulphonate (Leuller and Pomme, 1930). This salt is obtained by the action of two molecules of sulphonic acid of benzene on a basic molecule in a solution of water with a slight acid excess; it is concentrated and allowed to crystallize. The product is washed with alcohol which eliminates the excess of sulphobenzoic acid. For the sake of consistency I have expressed the results in oxydimorphine hydrochloride.

(a) *Subcutaneous injection.* The strength of the solution of oxydimorphine benzoic sulphonate, expressed in oxydimorphine hydrochloride, is 3.62 per cent. The injections are made in the flanks, and the percentages of mortality, after twenty-four hours, are as follows:

Determination of the toxicity of oxydimorphine hydrochloride administered to rats by subcutaneous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
362	4	20
579	4	30
640	10	50
724	10	100

Average variation for the 50 per cent lethal dose: 16.

50 per cent lethal dose of oxydimorphine hydrochloride administered by subcutaneous injection: 640±90 δ per g.

Percentage of error: 14 per cent.

(b) *Intravenous injection.* The strength of the solution of oxydimorphine benzoic sulphonate expressed in hydrochloride is 1.8 per cent in physiological serum. The injection is made in the internal saphena of a hind foot, and the rats are examined after twenty-four hours. The percentages of mortality are as follows:

Determination of the toxicity of oxydimorphine hydrochloride administered to rats by intravenous injection

Dose (δ per g.)	*Number of animals*	*Mortality percentage*
24	3	0
30	4	0
45	4	0
91	10	30
108	10	60

Average variation for the 50 per cent lethal dose: 16.

50 per cent lethal dose administered by intravenous injection: 102 ± 14 δ per g.

Percentage of error: 14 per cent.

(c) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* This ratio for oxydimorphine hydrochloride is 6.5. Although weaker than it is with mice, it is greater than that found for morphine. According to Jeanne Lévy (1945), oxydimorphine is converted more rapidly than morphine in the rat's organism into a substance less toxic than itself. The 50 per cent lethal doses of morphine and oxydimorphine are identical when injected intravenously, but different when injected subcutaneously, oxydimorphine being less toxic than morphine.

(3) *Daily injection of morphine in rats*

The animals are placed four or five in a group in glass crystallizers 250 mm. in diameter covered by a lid with a grill. The glass bowls are cleaned twice a week and strewn with wood shavings. The food, changed every day, consists of cereal grains (wheat, barley, oats) moistened bread and, twice a week, boiled potatoes. A 150 c.c. flask filled with water is fixed to the lid, the narrow neck enabling the rats to take in the water directly drop by drop. The bowls are placed in a ventilated room kept at a constant temperature of 21°C. The rats used, males and non-pregnant females, are three to three-and-a-half months old and weigh from 75 to 110 g. The flanks of the animals are shaved before the beginning of the experiment, the subcutaneous injections are made in each flank alternately, and they are washed in 60° alcohol before and after the injection.

First experiment: Twenty-one rats received increasing doses of morphine hydrochloride every day (except Sunday) for seven weeks. [11]

(a) *Doses.* I chose as an initial dose a quantity equivalent to 40 per cent of the 50 per cent lethal dose for subcutaneous injection: 0.100 mg. per g. That quantity of morphine does not cause death in normal rats. I increased that dose by 0.100 mg. per g., or 4 per cent of the 50 per cent lethal dose, daily for seven weeks. At the end of the seventh week, the quantity injected amounted to 0.500 mg. per g.: or 200 per cent of the 50 per cent lethal dose.

The concentrations of the solutions varied in terms of the dose, in accordance with the proportions set forth in the table below:

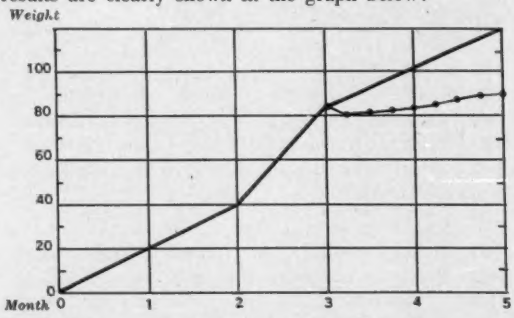
Concentrations of the solutions of morphine hydrochloride in relation to doses injected

Number of weeks	*Doses (in δ per g.) at the beginning of each week*	*Concentrations of the solutions (Percentages)*
1	100	1
2	160	2
3	220	2
4	280	3
5	340	4
6	400	4
7	460	4

[11] In the remainder of the experiment these animals will be designated as group III.

(b) *Behaviour of the animals.* The rats become drowsy half an hour after the injection of morphine. This state, which lasts two or three hours, is observed during the first three days of the experiment. On the fourth and fifth days, the animals, although not drowsy, nevertheless find difficulty in standing. This state appears twenty to thirty minutes after the injection and lasts for an hour. From the second week onwards, the injection no longer affects their behaviour, although the quantity of morphine injected is 60 per cent larger than the initial quantity. Thus, there is habituation to the depressive action of morphine.

(c) *Growth of the animals.* The daily administration of morphine prevents the regular growth of the rats. The average weight of a three-month-old rat is 85 g.; at five months the adult animal weighs an average of 120 g. The weight of the rats subjected to the experiment varies little during the seven weeks of daily injections with morphine. A rat weighing 85 g. at the beginning of the experiment weighs 91 g. two months afterwards. These results are clearly shown in the graph below:



Graph of the average growth of normal rats and of those receiving daily injections of morphine hydrochloride from the third month onwards. From the third to the fifth month, the points show the average weight of the animals subject to the experiment each week.

(d) *Mortality during the experiment.* The total mortality was eleven rats out of twenty-one, or about 50 per cent. The animals died regularly from the second week of the experiment onwards, as the following table shows:

Mortality of the rats (in terms of the doses injected)

Number of weeks	*Doses in δ per g. injected at the end of each week*	*No. of deaths each week*
1	150	0
2	210	1
3	270	2
4	330	1
5	390	3
6	450	1
7	500	3

(e) *Toxicity of morphine.* Owing to the small number of animals surviving, I found it impossible in this preliminary experiment to establish accurately the 50 per cent lethal dose. The experiments gave the following results:

(∝) When injected subcutaneously, the animals at least tolerated 0.300 mg. per g., or twice the 50 per cent lethal dose for normal rats.

(β) With the intravenous method, the 2 per cent solution of morphine hydrochloride in physiological serum was injected in the internal saphena of a hind foot; and the mortality was as follows:

Toxicity of morphine hydrochloride administered to habituated rats by intravenous injection

Doses (in δ per g.)	*Number of animals*	*Mortality percentage*
100	5	0
150	4	20
175	4	100

As the dose of 0.100 mg. per g. did not cause any mortality, the surviving animals were used twenty-four hours after the general injection of morphine and increasing doses were administered to them.

(f) *Summary.* Rats are able to tolerate daily increasing doses of morphine hydrochloride administered subcutaneously until these reach twice the 50 per cent lethal dose for normal animals. As rats appear to become habituated to morphine, I continued the experiments.

Second experiment. This was carried out with sixty-three rats, males and non-pregnant females, under laboratory conditions identical with those of the first experiment,[12] except with respect to the concentrations of the solutions; for when quantities less than 1 c.c. are injected, mortality is reduced and only amounts to 14 per cent. The following table shows the concentrations of the solutions in relation to the doses and the number of deaths per week:

Concentrations of the solutions and weekly mortality in relation to the doses of morphine hydrochloride injected

Number of weeks	*Doses (in δ per g.) at the beginning of each week*	*Concentrations of morphine hydrochloride solutions (Percentages)*	*Number of deaths weekly*
1	100	2	0
2	160	3	2
3	220	4	0
4	280	4	2
5	340	4	1
6	400	5	2
7	460	6	1
8	500	8	1

(4) *Determination of the 50 per cent lethal dose of morphine hydrochloride administered by subcutaneous and intravenous injection to rats habituated to morphine*

(a) *Subcutaneous injection.* The 4 per cent solution of morphine hydrochloride was administered to the rats of the second experiment after they had received 0.500 mg. per g. on the previous day. The table below shows the mortality percentage obtained in twenty-four hours in relation to the doses injected.[13]

Determination of the toxicity of morphine hydrochloride administered by subcutaneous injection to rats habituated to morphine

Doses (in δ per g.)	*Number of animals*	*Mortality percentage*
600	5	0
650	5	0
700	5	0
750	6	0
800	10	50

[12] These animals will be referred to as group III.

[13] During the experiment the animals not used for the determination of toxicity continue to receive 0.500 mg. per g. daily.

Average variation for the 50 per cent lethal dose: 16.

50 per cent lethal dose of morphine hydrochloride administered by subcutaneous injection to rats habituated to morphine for seven weeks: 800 ± 10 δ per g., or 320 per cent of the dose 50 per cent lethal to normal animals.

Percentage of error: 1.2 per cent.

(b) *Intravenous injection.* The injection is administered in the internal saphena of a hind foot with a 2 per cent solution of morphine hydrochloride in physiological serum. The mortality percentages twenty-four hours after the injection of morphine appear in the table below.[14]

Determination of the toxicity of morphine hydrochloride administered by intravenous injection to rats habituated to morphine

Doses (in δ per g.)	*Number of animals*	*Mortality percentage*
100	5	0
150	10	10
160	5	20
170	6	100
175	4	100

Average variation for the 50 per cent lethal dose: 16.

50 per cent lethal dose of morphine hydrochloride administered by intravenous injection to habituated animals: 164 ± 19 δ per g., or 164 per cent of the dose 50 per cent lethal to normal animals.

Percentage of error: 11.5 per cent.

(c) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* In rats this ratio amounts to 4.8. Rats are able to tolerate by subcutaneous injection a dose equivalent to more than three times the dose toxic for normal animals and by intravenous injection a dose equivalent to more than 1.5 times the dose toxic for normal animals. Furthermore, since the ratio of toxicities according to the method of injection is 4.8, morphine seems to undergo a more rapid conversion in the organisms of rats habituated to the drug than in those of animals which have not been injected. It approaches the similar ratio obtained with oxydimorphine.

Control experiment. In order to ascertain whether tolerance of morphine is not caused by the effect of the injection alone, twenty-four rats were administered 0.33 c.c. of distilled water subcutaneously daily for three weeks. After that period, the 50 per cent dose of morphine hydrochloride injected subcutaneously was determined in the case of ten of these rats.

Mortality amounted to 50 per cent for 0.250 mg. per g., and is therefore identical with that obtained with normal animals.

This experiment confirms that tolerance of large doses of morphine is due to the effect of the repeated injections of morphine hydrochloride.

[14]During the experiment the animals not used for the determination of toxicity continue to receive 0.500 mg. per g. daily.

(5) *Different methods of administering the drug*

I wished to determine the speed with which rats are able to tolerate toxic doses of morphine. I shall describe below the various experiments carried out on groups of animals submitted to chronic intoxication of greater or less intensity for varying lengths of time.

Group I (three days). Subcutaneous injections of 0.100 mg. of morphine hydrochloride per g. of weight are administered to thirty rats for three consecutive days. A 2 per cent concentration of the solution is used. The toxicities are determined on the fourth day. The mortality observed in relation to the doses and the methods of injection are summed up in the table below:

Toxicity of morphine hydrochloride administered by subcutaneous and intravenous injection to rats of group I

Doses (in δ per g.)	*Number of animals*	*Mortality percentage*
Subcutaneous injection:		
600	6	0
800	6	18
Intravenous injection:		
150	6	18
160	5	20
170	2	100

These rats tolerate the same doses (0.800 mg. per g. with subcutaneous injection, 0.165 mg. per g. with intravenous injection) as animals habituated to morphine for seven weeks. This tolerance of large doses appeared to be surprising, but I was able to confirm this phenomenon by numerous trials.

Group II (three weeks). Very rapidly increasing doses of morphine hydrochloride were administered by subcutaneous injection to fifty-four rats daily (except Sundays). The appended table shows the successive doses injected, the concentrations of the solutions, the number of animals to which injections were administered and the mortality. A dose of 0.500 mg. per g. is reached, and is then administered daily to a number of rats, while others are given increasing doses in order to determine the maximum quantity tolerated.

The low mortality proves that rats become habituated very rapidly to morphine. After receiving injections for twenty-eight days, four rats tolerated four times the dose 50 per cent lethal to normal animals.

Mortality according to the number of animals injected and concentrations of the solutions in relation to doses

Number of weeks	*Doses in δ per g.*	*Concentrations (Percentages)*	*Number of animals injected*	*Number of deaths*
1	100	2	54	
	120	2	54	
	140	2	54	
	160	4	53	1
	180	4	53	
	200	4	53	
2	220	4	53	
	250	4	53	
	300	6	53	
	350	6	53	
	400	8	53	
	450	8	52	1

Number of weeks	Doses in δ per g.	Concentrations (Percentages)	Number of animals injected	Number of deaths
3	500	8	51	
	550	8	15	
	600	8	15	
	650	8	13	
	700	8	13	
4	750	8	13	1
	800	8	12	1
	850	8	11	1
	900	8	5	1
	1,000	8	4	0

On the basis of the results obtained with these groups I and II, it might seem unnecessary to habituate the rats for more than three weeks or even three days. This method, however, points to certain observations, as I shall show in connexion with the wearing off of the analgesic action and with elimination.

Group III (seven weeks). The method of administration and the toxicities of morphine in this group of rats has been described on pages 30 and 31. These are the animals to which injections of doses ranging from 0.100 to 0.500 mg. per g., increased each day by 0.010 mg. per g., were administered for seven weeks.

Group IV (twelve weeks). These rats are those in group III which continue to receive daily, for five weeks, 0.500 mg. of an 8 per cent morphine hydrochloride solution per g. of body weight. At the end of the tenth week the rats, with numerous scars on their flanks and rapidly diminishing weight, are dying. After twelve weeks, the animals have scars and dull shaggy fur and take very little food. The mortality rate rises. With a dose of 0.500 mg. per g., it seems difficult to keep them alive beyond this period.

Summary: The various methods of administering the morphine to the rats were as follows:

Group I: Rats receiving a subcutaneous injection of 0.100 mg. of morphine hydrochloride per g. for three consecutive days.

Group II: Rats receiving subcutaneous injections of rapidly increasing doses of morphine hydrochloride over a period of three weeks.

1st week:	0.10;	0.12;	0.14;	0.16;	0.18;	0.20;	mg. per g.
2nd week:	0.22;	0.25;	0.30;	0.35;	0.40;	0.45;	mg. per g.
3rd week:	0.50;	0.50;	0.50;	0.50;	0.50;	0.50;	mg. per g.

Group III: Rats receiving subcutaneous injections of doses of morphine hydrochloride increasing by 0.01 mg. per g. daily for seven weeks.

Initial dose: 0.10 mg. per g.
Final dose: 0.50 mg. per g.

Group IV: Rats receiving subcutaneous injections of doses of morphine hydrochloride increasing by 0.01 mg. per g. daily, for twelve weeks.

Initial dose: 0.10 mg. per g.

The dose of 0.50 mg. per g. is reached seven weeks after administration of the drug begins, and the rats continue to receive this injection for five weeks.

Tolerance to toxic doses of morphine develops very quickly in rats. Three successive injections (group I) enable them to tolerate three times more morphine than the normal animal. The daily administration, for three or seven weeks (groups II and III), of increasing doses of morphine makes them capable of tolerating doses four times greater than the normal rat. However, tolerance to large doses does not extend beyond twelve weeks (group IV). The ratio of toxicity according to the method of introduction (subcutaneous and intravenous), which is higher in the animal habituated to the drug than in the normal animal, might indicate a more rapid transformation of the morphine into a less toxic substance in the organism of the habituated animal.

B. *Physical condition of rats habituated to morphine*

This study relates to the behaviour of rats in groups II and III.

(1) *Depressive effect of morphine*

In normal rats, small doses of morphine hydrochloride (0.100 mg. per g.), given by subcutaneous injection, induce drowsiness twenty minutes after the injection, and this state continues for two to three hours.

Larger doses (0.300 mg. per g.) produce, in addition to drowsiness, diminishing frequency of respiratory movement and increased depth of respiration. Death occurs in one to two hours.

In habituated rats, drowsiness after injection only appears for the first three to five days. In the second week, the rat shows no depressive symptoms after the injection, behaves like an animal which has not been injected and takes food normally.

Very large doses (0.500 mg. per g.), always induce a state of agitation in habituated animals for one to two hours after the injection. The slightest noise makes them start.

(2) *Growth*

As stated previously (page 31), growth is arrested by the regular administration of morphine hydrochloride. The following table gives, by way of example, the weights of three rats before the experiment and seven weeks later.

Weights of three rats before the beginning of the experiment and after seven weeks of regular injections

Weight before experiment (in g.)	Weight (in g.) 7 weeks later (dose injected 0.500 mg/g.)
82	95
84	82
105	109

(3) *Reproduction*

The male and female genital organs of habituated rats become atrophied. The testicles and seminal vesicles lose

50 to 75 per cent in weight, and the spermatozoa disappear. In females, the uterine cornua become filiform and the ovaries have no ripe follicles. I have never noted any case of pregnancy when males and females have been put together in the same bowl.

C. *Diminution of analgesic action during habituation*

The test used to study this subject was that described by Mme. Buchel and Jeanne Lévy (1948-1949). This test, which was carried out on rats in order to compare the analgesic effect of various drugs, enabled me to trace, during the period of habituation, the analgesic effect of an initial active dose of morphine on the normal rat, and to determine the dose needed to induce the same state during the progress of habituation.

The analgesic power of various doses of morphine hydrochloride according to the method of introduction (subcutaneous and intraperitoneal) was first determined in normal rats.

(1) *Description of the test*

The rat is tied on its back to a board by its feet and head. In this uncomfortable position it squeals and struggles. Morphine hydrochloride is administered. The length of time needed for the squealing on the one hand and the spontaneous struggling on the other to subside (shown in the tables by — +) is noted and corresponds to a state of slight analgesia; the length of time needed for the rat to fail to react, either by squealing or struggling, to a strong pinching of the tail with Kocher's forceps (shown in the tables by —), is noted and corresponds to a state of deep analgesia. The duration represents the length of time in which the animal remains in the — state.[15]

(2) *Determination of the analgesic effect of morphine hydrochloride on normal rats*

I give below, as an example, the calculation of the degree of analgesia produced in relation to the dose of morphine hydrochloride administered by subcutaneous and intraperitoneal injection; it was carried out on normal rats, males and non-pregnant females, aged from three to four months, and weighing 80 to 120 grammes. Each dose represents the mean effect observed in series of six animals. A 1 per cent solution of morphine hydrochloride was used.

[15]The duration of the + — state varies; in some experiments, it may be several hours before the rats squeal or struggle.

Analgesic effect of morphine (according to L. Buchel and Jeanne Lévy, 1949)

		Squealing			Agitation		
	Dose injected (in δ per g.)	Period of latency (min.) — +	—	Duration (min.)	Period of latency (min.) — +	—	Duration (min.)
Subcutaneous	25	24	26	27	32	47	10
	50	24	37	59	19	34	17
	100	19	32	48	21	22	21
	125	18	28	137	18	38	31
	150	12	28	145	22	32	105
Intraperitoneal	25	15	37	15	30	0	0
	50	14	24	50	18	40	19
	100	6	11	88	10	19	49
	150	1	5	110	5	10	65
	200	1	15	170	15	20	92

Each calculation must be carried out on a rat which has never received analgesia, since the animal reacts less well to an active dose of morphine as soon as it has received a first injection.

The injections must be separated by a period of seven to fourteen days if the rat is to show constant behaviour towards morphine hydrochloride.

Analgesic effect of morphine on groups of four rats, injected after varying intervals. Intraperitoneal injection 0.10 mg. per g.

	Squealing			Agitation		
Time separating 2 injections (in days)	Period of latency (min.) — +	—	Duration (min.)	Period of latency (min.) — +	—	Duration (min.)
0	3½	7½	108	3½	7½	50
2	4	11	70	4	11	15
0	3½	8½	137	3½	8¼	49
7	3½	9½	79	3½	9½	57
0	3	10	96	3	10	45
14	4	8	150	6	19	34

(3) *Determination of the analgesic effect of morphine hydrochloride on rats under morphine treatment*

The analgesic effect of morphine hydrochloride on rats is determined by administering the drug in steadily increasing doses, the initial dose being 0.100 mg. per g. This initial dose of 0.100 mg. per g. selected for intra-

peritoneal injection induces a period of analgesia in a normal rat sufficiently prolonged to enable its effect to be determined at the outset of the period of habituation.

(a) *Analgesic effect of morphine on rats in group I.* This is measured for three days on five rats after intraperitoneal injection of 0.100 mg. per g. and on the fourth day on the same animals after intraperitoneal injection of 0.300 mg. per g. It can be seen from the following table that the period of analgesia regularly diminishes on the first three days and is still shorter on the fourth day after the injection of a dose three times greater than the original dose.

Determination of the analgesic effect of morphine hydrochloride administered by intraperitoneal injection over a period of four consecutive days

Number of days	Dose injected (in δ per g.)	Squealing: Period of latency (min.) —	Squealing: Period of latency (min.) +	Squealing: Duration (min.)	Agitation: Period of latency (min.) —	Agitation: Period of latency (min.) +	Agitation: Duration (min.)
1	100	2 1/3	9	94	2 1/3	9	60
2	100	2 1/4	7 1/4	75	2 1/4	9	40
3	100	4	8	31	5 1/2	7 1/2	13
4	300	3	11	22	8	4	6

(b) *Analgesic effect of morphine on rats in group II.* This action was determined by administering rapidly increasing doses of morphine hydrochloride by subcutaneous injection to twelve rats before habituation began. Analgesia is first measured after intraperitoneal injection of 0.100 mg. per g. into normal rats, and is then measured in the same animals after the drug has been administered for three successive days. The analgesic effect is then observed in the same rats after eleven and twenty days of injection, the doses of morphine hydrochloride administered by intraperitoneal injection at the time of measurement being 0.200, 0.300 and 0.400 mg. per g. It is clear from the following table of the average results obtained that the duration of analgesia regularly diminishes over the period of twenty days, morphine no longer having any analgesic effect at the end of that period, despite the increase in the dose of the intraperitoneal injection to four times that of the original injection.

Determination of the analgesic effect of morphine hydrochloride administered to rats in group II by intraperitoneal injection

Doses injected 24 hours before test (in δ /g.)	Doses administered by intraperitoneal injection (in δ /g.)	Squealing: Period of latency (min.) —	Squealing: Period of latency (min.) +	Squealing: Duration (min.)	Agitation: Period of latency (min.) —	Agitation: Period of latency (min.) +	Agitation: Duration (min.)
0	100	4	7	131	4	7	76
140	100	6	17	34	6	0	0
240	200	9	35	13	9	0	0
450	300	6	0	0	0	0	0
500	400	3	0	0	3	0	0

(c) *Analgesic effect of morphine on rats in group III.* Analgesic action is observed in four rats after intraperitoneal injection of 0.100 mg. per g. Daily increasing doses of morphine hydrochloride are then administered to these rats by subcutaneous injection, the initial dose being 0.100 mg. per g., increasing daily by 0.010 mg. per g.

The following table shows the average increase in the period of latency and the average decline in the duration of analgesia in the four rats during the period of habituation, the rats being examined each week after the intraperitoneal injection of 0.100 mg. of morphine hydrochloride per g. of body weight.

Determination of the analgesic effect of morphine hydrochloride administered by intraperitoneal injection in a dose of 0.100 mg. per g. to rats during the first three weeks of habituation

Doses injected 24 hours before test (in δ /g.)	Doses administered by intraperitoneal injection (in δ /g.)	Squealing* Period of latency (min.) —	Squealing* Period of latency (min.) +	Squealing* Duration (min.)	Agitation* Period of latency (min.) —	Agitation* Period of latency (min.) +	Agitation* Duration (min.)
Normal	100	5	12	110	5	15	45
170	100	5	15	45	15	0	0
230	100	15	50	10	20	0	0
300	100	30	0	0	0	0	0

*All figures represent the average results obtained by experiment.

No further analgesic effect being observed with the original dose of 0.100 mg. per g. of morphine hydrochloride, the dose of the intraperitoneal injections is increased every eight or fifteen days. It can be seen from the following table that the increasing quantities of the drug injected to measure the analgesia reduce the

period of latency before the cessation of spontaneous squealing. Injections of 0.450 and 0.500 mg. per g., however, still eliminate spontaneous agitation, as well as squealing when the tail is pinched, without producing profound analgesia in highly habituated rats.

Determination of the analgesic effect of increasing doses of morphine hydrochloride administered by intraperitoneal injection to rats during the fourth, fifth, sixth, seventh, eighth, ninth and tenth weeks of habituation

Doses injected 24 hours before test (in δ /g.)	Doses administered by intraperitoneal injection (in δ /g.)	Squealing* Period of latency (min.) — +	—	Duration (min.)	Agitation* Period of latency (min.) — +	—	Duration (min.)
350	200	15	0	0	0	0	0
400	200	15	0	0	0	0	0
460	300	20	0	0	0	0	0
520	300	10	0	0	0	0	0
580	400	10	0	0	0	0	0
620	450	5	20	15	15	0	0
680	500	20	30	15	60	0	0

*All figures represent the average results obtained by experiment.

The effect of larger doses could not be determined because of their toxicity.

The 50 per cent lethal dose of morphine hydrochloride administered by intraperitoneal injection is 0.225 mg. per g. in normal animals and 0.600 mg. per g. in habituated animals.

Summary. The reduction and even the disappearance of the analgesic effect of morphine is similar in the case of the rats in groups II and III.

In the case of the rats in group I, the analgesic effect of morphine diminishes but has not disappeared on the fourth day; there is no parallelism between the two main tests used to define habituation — tolerance of toxic doses and reduction of the analgestic action.

In the case of the rats in groups II and III, on the other hand, the two tests to determine habituation produce comparable results.

D. *De-habituation*

This was studied in the rats in groups II and III for which the last injection of morphine hydrochloride was 0.500 mg. per g.

(a) *Agitation.* Non-injected animals show signs of agitation on the second and third days after discontinuance of the drug and endeavour to bite if any attempt is made to catch them. On the fourth day this agitation disappears completely.

(b) *Weight.* The weight of the rats diminishes for forty-eight hours after the last injection, remains unchanged on the third and fourth days and begins to increase on the fifth day. Twenty per cent of the animals, however, become very thin and die four days after discontinuance of the drug. These results are shown in the following table:

Weight of rats after discontinuance of morphine hydrochloride

Weight at time of last injection (in g.)	Weight during the period in which morphine is discontinued 2 days	3 days	4 days	5 days
109	100	100	98	103
113	100	98	92	100
121	102	100	100	105
115	97	84	D	–
119	114	103	98	100
103	98	79	D	–

(c) *Tolerance of morphine.* The rats are able to tolerate an initial dose of 0.500 mg. per g. if the period for which the drug is withheld does not exceed five days. Beyond that period they all die without exception when such a dose is administered.

(d) *Analgesia.* The analgesic effect of morphine is studied during the process of de-habituation.

A number of rats in group II which have been given a final dose of 0.500 mg. per g. of morphine hydrochloride are given an initial dose of morphine (0.100 mg. per g.) by intraperitoneal injection seven, fourteen and twenty-five days after discontinuance of morphine. Analgesic action was slight after seven days, stronger after fourteen days and almost normal after twenty-five days. The following table shows in brief the average analgesic effect on normal rats of 0.100 mg. per g. administered by intraperitoneal injection, the analgesic effect of 0.400 mg. per g. on rats habituated for a period of three weeks, and the analgesic effect after injection of 0.100 mg. per g. into the same rats seven, fourteen and twenty-five days after discontinuance of the drug.

Determination of the analgesic effect of morphine hydrochloride, administered by intraperitoneal injection, on rats after the withdrawal of morphine

Doses injected 24 hours before test (δ per g.)	Number of days after withdrawal	Doses by intraperitoneal injection (δ per g.)	Squealing Period of latency (min.) — +	—	Duration (min.)	Agitation Period of latency (min.) — +	—	Duration (min.)
Normal		100	4	7	131	4	7	76
500		400	3	0	0	3	0	0
	7	100	4	23	46	17	0	0
	14	100	3	10	72	3	14	15
	25	100	6	13	110	7	22	34

Fourteen days after the withdrawal of the morphine, the analgesic effect is still weak and it takes at least twenty-five days for the effect to approach normal. Habituated rats behave differently from normal rats, in which the original analgesic effect reappears between seven and fourteen days after the injection.

E. *Reaction to hypnotics of rats habituated to morphine*

This study was carried out in order to show that a strongly habituated animal may fail to show cross habituation to hypnotics.

Research into the wearing off of the effect of hypnotics on animals habituated to morphine has led scientists to contradictory results. Biberfeld (1916) with veronal, Myers (1916) using chloral, amylene hydrate and gardenal, did not observe clear habituation to these drugs in animals habituated to morphine. On the other hand, Tatum, Collins and Seevers (1929) found that the effect of barbiturates was less on habituated animals than on normal animals. L. Buchel having recorded modifications in the duration of sleep induced in normal rats by evipan, after previous injection of morphine, I resumed in collaboration with her this study of habituated rats.

I chose two barbiturates, evipan (N-methyl-methyl-cyclo-hexenyl-5-5-barbituric acid) and soneryl (butyl-ethyl-barbituric acid), the first inducing, in normal rats, a short and immediate period of sleep and the other a longer period of sleep induced after a certain period of latency.

(1) *Behaviour of normal rats under the influence of evipan*

The three-months-old rats receive a subcutaneous injection of morphine hydrochloride, dose 0.050 or 0.200 mg. per g., or two successive injections of morphine hydrochloride at an interval of four hours, doses 0.035 mg., 0.050 mg., 0.075 mg. or 0.100 mg. per g. Four hours and forty-eight hours after the last dose of morphine hydrochloride, they are given an intravenous injection of sodium evipan, dose 0.025 mg. per g. The average period of sleep induced by the same dose of evipan in rats of the same age which have not received a previous injection of morphine is six minutes.

Average duration of sleep induced by intravenous injection of 25 δ per g. of sodium evipan, in rats which have been given one or two successive subcutaneous injections of morphine hydrochloride*

Number of injections	*Morphine doses (δ per g.)*	*Average duration of sleep induced by evipan*		
		4 hours after morphine (min.)	*48 hours after morphine (min.)*	*Control (min.)* 6
1	50	6½	6½	
	200	15	6½	
2	35	9½	6	
	50	10	6	
	75	10½	10½	
	100	24	8½	

* The experiments were carried out on groups of five rats, and the figures represent the average result obtained.

A prolongation of the period of sleep induced by evipan is observed in rats receiving two successive doses of morphine hydrochloride at an interval of four hours. The largest doses, 0.075 and 0.100 mg. per g., induce a slight prolongation of the period of sleep due to evipan forty-eight hours after the morphine.

If the evipan is injected after a single dose of morphine, the prolongation of the period of sleep after the largest dose of morphine (0.200 mg. per g.) is less than in the case of rats receiving two injections of 0.100 mg. per g. of morphine hydrochloride.

(2) *Behaviour of habituated animals under the influence of evipan*

The same experiment is carried out on habituated rats. These are given increasing doses of morphine hydrochloride for seven weeks, according to the experimental procedure described for group III, the last dose injected being 0.500 mg. per g. The injections of sodium evipan (0.025 mg. per g.) are given four, twenty-four and forty-eight hours after the last injection of morphine hydrochloride. At the same time, normal rats of the same age are given the same dose of evipan, which produces an average period of sleep of six minutes. The average period of sleep induced by evipan in the habituated rats is greater as compared with control rats when the evipan is injected four hours after the morphine. The increase in the period of sleep is smaller when the evipan is injected twenty-four hours after the morphine. The period of sleep induced by evipan is identical with that of the control animals when the evipan is injected forty-eight hours after the morphine.

The following table gives these results:

Average duration of sleep (minutes) induced by the intravenous injection of 25 δ per g. of sodium evipan in habituated rats*

Morphine (δ per g.) in habituated rats; last injection	*Time lapse between morphine injection and evipan (h.)* —	*Average duration of sleep in habituated rats (min.)*	*Average duration of sleep in controls (min.)* 6
500	4	13	
500	24	11	
500	48	6	

* Experiments carried out on groups of five rats. The figures represent the average result obtained.

The average period of sleep induced by evipan is slightly less in habituated rats four hours after the administration of 0.500 mg. of morphine hydrochloride per g. than in normal rats four hours after a single injection of 0.200 mg. per g. or two successive injections of 0.100 mg. per g. Forty-eight hours after the morphine, the average period of sleep induced by evipan is identical in the control animals and in the habituated rats, while it is slightly longer in normal animals which have been given an injection of 0.200 mg. per g. or two injections of 0.075 and 0.100 mg. per g.

There is no cross habituation.

(3) *Behaviour of normal rats under the influence of soneryl*

Three-months-old rats are given a subcutaneous injection of morphine hydrochloride, dose 0.200 mg. per g., or two successive injections of morphine hydrochloride at an interval of four hours, doses 0.035 mg., 0.050 mg., 0.075 mg. and 0.100 mg. per g. They are given an intravenous injection of 0.050 mg. per g. of soneryl, four hours and forty-eight hours after the last dose of morphine. The average duration of sleep[16] induced by the same dose of soneryl in rats of the same age which have not received a previous injection of morphine is twenty-eight minutes; individual variations are quite large, oscillating between thirteen and forty-one minutes. Sleep is not immediate and the average period of latency is five minutes; the limits of the period of latency are two to twenty-one minutes.

Average duration of sleep and of latency induced by the intravenous injection of 50 δ per g. of soneryl in rats having received one or two successive injections of morphine hydrochloride (subcutaneous)*

Morphine, number of injections	Doses δ per g.	Period of latency (min.) 4 hours after morphine	Period of latency (min.) 48 hours after morphine	Duration of sleep (min.) 4 hours after morphine	Duration of sleep (min.) 48 hours after morphine	Controls** Period of latency	Controls** Sleep (min.)
						5	28
1	200	0	3	117	27		
2	35	2 1/3	2 3/4	39 1/2	40 3/4		
	50	1/2	6	106	36		
	75	1/4	4 1/4	98	44		
	100	0	4 1/2	74	27		

* The experiments were carried out on groups of five rats.
** The experiments were carried out on twenty-eight rats.

An injection of 0.200 mg. per g. of morphine hydrochloride does not alter the length of sleep caused by soneryl. After the injection of two doses of 0.050, 0.075 and 0.100 mg. per g., the period of sleep caused by soneryl is increased if the soneryl is injected four hours after the morphine, but the period of sleep caused by soneryl injected forty-eight hours after the morphine is similar to that observed in the control rats.

(4) *Behaviour of habituated rats under the influence of soneryl*

The same experiment is carried out with habituated rats which have received constant doses of morphine hydrochloride varying from 0.100 mg. to 0.500 mg. for three weeks (rats in group II). Doses of 0.050 mg. of soneryl are administered intravenously four, twenty-four and forty-eight hours after 0.500 mg. of morphine hydrochloride per g. The average period of sleep caused by soneryl is much increased when the injection is made four hours after the morphine, but it is similar to that of the control rats twenty-four and forty-eight hours after the morphine.

The average length of sleep caused by soneryl is approximately the same in habituated rats having received 0.500 mg. of morphine hydrochloride per g. and in normal rats having received a single injection of morphine at 0.200 mg. per g. of morphine or two injections of 0.050 and 0.075 mg. per g. There again there is here no cross habituation.

Average duration of sleep and of the period of latency caused by intravenous injection of 50 δ per g. of soneryl in habituated rats*

Morphine, last injection (in δ per g.)	Lapse of time between injection of morphine and soneryl (h)	Period of latency (min.)	Duration of sleep (min.)	Controls** Period of latency (min.)	Controls** Duration of sleep (min.)
				5	28
500	4	1/3	115		
500	24	4	30		
500	48	4 3/4	18 1/2		

* Experiments were carried out on groups of five rats.
** Experiments were carried out on twenty-eight rats.

Summary. The reaction of habituated rats to the two hypnotics studied is not very different from that of normal rats having received one or two preliminary injections of morphine. In those two groups of animals the average duration of sleep is prolonged, and it cannot therefore be supposed that cross habituation has been established.

F. *Habituation to heroin*

I studied habituation to heroin by determining, as in the case of morphine, the tolerance of toxic doses in the normal animal and in the animal having received repeated injections of heroin.

[16] The experiments were carried out on twenty-eight rats.

In a second series, I examined the analgesic effects of heroin and the behaviour of rats habituated to heroin under the influence of evipan.

(1) *Determination of the 50 per cent lethal dose of diacetylmorphine hydrochloride administered by subcutaneous and intravenous injection to normal rats*

(a) *Subcutaneous injection.* Male and non-pregnant female animals aged three months are injected in the flank with a 2 per cent solution of diacetylmorphine hydrochloride (heroin). The results are as follows:

Doses in δ per g.	*Number of animals*	*Mortality percentage*
50	4	0
60	6	0
70	6	50
125	6	80
150	6	100

Average variation: 20.

50 per cent lethal dose by subcutaneous injection: 70± 25 δ per g.

Percentage of error: 35 per cent.

(b) *Intravenous injection.* A 4 per cent solution of diacetylmorphine hydrochloride in physiological serum, is injected into the internal saphena of a hind foot. The mortality percentages for the various doses are shown in the following table:

Determination of the toxicity of heroin administered by intravenous injection

Dose in δ per g.	*Number of animals*	*Mortality percentage*
20	5	20
25	8	25
27	6	33
30	15	75

Average variation: 17.

50 per cent lethal dose of diacetylmorphine hydrochloride administered by intravenous injections: 28 ± 4.3 δ per g.

Percentage of error: 15 per cent.

(c) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* This ratio for diacetylmorphine hydrochloride amounts to 2.5 and appears to indicate that heroin like morphine only undergoes slow changes in the organism.

(2) *Daily administration of heroin to rats*

Diacetylmorphine hydrochloride was administered to rats: (a) in constant small doses (0.010 mg. per g.); (b) in increasing doses.

(a) *Administration of constant doses of heroin.* Twelve rats, males and non-pregnant females, aged three months, received daily subcutaneous injections of a dose not toxic for the normal animal. The injections were given over a period of nineteen days. The analgesic effect was determined every week as I shall show later. The concentration of the solution was 2 per cent and the dose injected was 0.010 mg. per g. Two of the rats died after the third dose and six out of ten rats after the nineteenth dose. The animals were in a drowsy state after each injection. Subcutaneous injections of 0.125 mg. per g. of diacetylmorphine hydrochloride and intravenous injections of 0.030 mg. per g. did not cause any deaths among the four surviving rats. Despite their low resistance to repeated injections of heroin, they withstood larger doses than those which would be toxic for normal animals, whether administered by subcutaneous or intravenous injection.

(b) *Administration of increasing doses of heroin.* Twenty-four rats, male and female, were given daily subcutaneous injections of increasing doses of diacetylmorphine hydrochloride. The initial dose was 0.010 mg. per g.; on the thirtieth day they received 0.070 mg. per g. The doses were increased daily by 0.002 mg. per g. After thirty days the injections were continued on a few rats which tolerated up to 0.100 mg. per g.; successive doses of 0.070, 0.075, 0.080, 0.090 and 0.100 mg. per g. were injected. During that final period, no deaths were observed.

The concentration of the solutions in relation to the doses and the mortality during the period of habituation of the rats are shown in the table below, together with the number of animals injected.

Concentration of solutions and mortality in relation to doses of heroin injected

Doses of heroin injected (δ per g.)	*Concentration of solution (percentage)*	*Number of animals injected*	*Number of deaths*
10	2	24	—
16	2	24	1
18	4	23	1
28	6	22	2
34	8	20	—
46	1	20	1
70	1	19	1
100	1	6	0

The animals behaved in exactly the same way as those to which morphine had been administered: they were drowsy the first four days after the injection, and in a normal state thereafter.

The growth of the animals is arrested by the daily administration of heroin.

(3) *Determination of the 50 per cent lethal dose administered by subcutaneous and intravenous injection*

(a) *Subcutaneous injection.* A 2 per cent solution of diacetylmorphine hydrochloride was injected subcutaneously in rats which had been given a last dose of 0.070 mg. per g. during the period of habituation. In view of the small number of animals surviving, they had to be given in succession the different doses of diacetylmorphine hydrochloride.

Determination of the toxicity of heroin administered by subcutaneous injection

Dose (δ per g.)	Number of animals	Mortality percentage
200	6	0
250	4	0
300	5	0
350	14	14
400	5	20
450	4	0
500	4	0
600	8	0
700	4	75

Average variation: 17.

50 per cent lethal dose of diacetylmorphine hydrochloride administered by subcutaneous injection: 666 ± 200 δ per g.

Percentage of error: 30 per cent.

(b) *Intravenous injection.* Injection of a 1 per cent solution of diacetylmorphine hydrochloride in a physiological serum in the internal saphena of a hind foot gave the following mortality percentages according to the dose:

Determination of the toxicity of heroin administered by intravenous injection

Dose (δ per g.)	Number of animals	Mortality percentage
30	5	20
40	5	20
45	8	25
50	5	100

Average variation: 17.

50 per cent lethal dose of diacetylmorphine hydrochloride administered by intravenous injection: 466 ± 66 units δ per g.

Percentage of error: 14 per cent.

(c) *Toxicity by subcutaneous injection/toxicity by intravenous injection.* This ratio for diacetylmorphine hydrochloride in rats habituated to the drug amounts to 14.2. Compared to the figure for normal animals, this high value seems to indicate a more rapid transformation of heroin in the organism of the rat habituated to the drug than in the normal animal.

Since the 50 per cent lethal doses by subcutaneous injection of heroin and morphine are almost the same for animals habituated to the drug, it seems likely that heroin undergoes an intermediary transformation into morphine through disacetylation. Wright (1940) observed, moreover, that heroin mixed with human serum is slowly disacetylated.

Summary. Rats can only tolerate a small but repeated dose of heroin for a few days. After nineteen daily injections of 0.010 mg. per g., however, they can tolerate a subcutaneous injection of a dose double that which would be toxic for the normal animal. Animals receiving increasing daily doses of heroin can tolerate a subcutaneous injection of a quantity of heroin ten times greater than that which would be toxic for the normal animal.

It may be said that from the point of view of toxicity[17] rats become habituated to heroin. They have a greater toleration of heroin than of morphine: they withstand subcutaneous injections of ten times more heroin and only four times more morphine than the normal rat. In man, toleration of heroin is also greater than toleration of morphine (Biggam, Arafa and Ragab, 1932).

(4) *Diminution of the analgesic effect during habituation*

The analgesic effect of heroin has been studied by means of the same test as that applied to morphine by L. Buchel and Jeanne Lévy (1949). Heroin is much more active than morphine, particularly the initial dose which, administered by interperitoneal injection is 0.007 mg. per g. for heroin and 0.025 mg. per g. for morphine.

(a) *Analgesic effect of heroin on the normal rat.* The table below shows the results obtained with this drug according to the method of injection.

[17] The figures represent an average of at least four experiments

Analgesic effect of heroin according to the method of injection (according to L. Buchel and Jeanne Lévy, 1949)

Dose injected (δ per g.)	Squealing* Period of latency (min.)		Duration (min.)	Agitation* Period of latency (min.)		Duration (min.)
	−	+		−	+	
Subcutaneous						
1.5	7	—	—	9	—	—
3.5	7	17	33	7	18	15
7	9	15	33	7	21	30
12.5	7	12	50	7	12	55
25	1	5	80	5	10	75
50	1	5	126	4	9	122
Intraperitoneal						
5	6	—	—	5	—	—
7	6	9	38	6	9	22
10	1	5	30	1	9	18
25	1	4	55	1	5	14
50	1	6	70	1	5	57
100	1	5	135	1	5	60

* The figures represent an average of at least four experiments.

The analgesic effect of heroin is more marked when the drug is injected subcutaneously. I carried out experiments on habituated rats with that type of injection. As the animal reacts less well after a second injection of heroin, in order to obtain equivalent analgesic reactions, injections should be given at least nine days apart.

(b) *Analgesic effect of heroin on rats receiving regular doses of the drug.* The analgesic effect was determined before the beginning of injections and twice during the period of habituation in rats injected with a constant dose of 0.010 mg. per g. of heroin and those receiving increasing doses.

A dose of 0.007 mg. per g.,[18] injected subcutaneously and having an analgesic effect of rather long duration, was administered before the beginning of habituation.

The analgesic effect was observed for the same drug after eight days of daily injections of the drug and the effect of a stronger dose (0.010 mg. per g.)[19] after a second period of eight days. The tables below show the analgesic effect on the groups of four rats examined.

[18] 1 per cent solution.

[19] 2 per cent solution.

Table I. Analgesic effect of heroin on rats receiving constant doses of the drug (0.010 mg. per g. daily)

Number of days during which heroin was administered	Doses (δ per g.) injected subcutaneously	Squealing* Period of latency (min.) —	Squealing* Period of latency (min.) +	Squealing* Duration (min.)	Agitation* Period of latency (min.) —	Agitation* Period of latency (min.) +	Agitation* Duration (min.)
0	7	7	12	124	10	17	81
7	7	7	10	60	8	25	20
14	10	4	9	50	7	15	40

* The figures represent the average of the experiments.

Table II. Analgesic effect of heroin on rats receiving increasing doses of the drug

Dose (δ per g.) injected before the test	Doses (δ per g.) injected subcutaneously	Squealing* Period of latency (min.) —	Squealing* Period of latency (min.) +	Squealing* Duration (min.)	Agitation* Period of latency (min.) —	Agitation* Period of latency (min.) +	Agitation* Duration (min.)
0	7	4½	9	115	5	13	66
25	7	5	11	24	20	—	—
55	10	5	9	30	4	11	9

* The figures given represent an average for all experiments.

The duration of deep analgesia diminishes even with a larger dose (0.010 mg. per g.) after fourteen days of regular administration.

The same dose of heroin administered to the animal before and after the injection of increasing doses for eight days causes a reduction in the duration of the analgesia after that period or eliminates the analgesic effect altogether, and increases the period of latency. A larger dose (0.010 mg. per g.) after fourteen days of regular administration of increasing doses still has some effect, but it is weak.

Summary. The analgesic effect diminishes during the habituation of rats to heroin. The diminution is greater in rats injected with increasing doses of the drug than in those to which a constant small dose is administered.

(5) *Behaviour of rats habituated to heroin under the influence of evipan*

L. Buchel studied the changes in the duration of sleep caused by evipan in normal rats having previously received two injections of heroin; we made the same study with rats habituated to heroin.

(a) *Behaviour of normal rats under the influence of evipan.* Injections of heroin are made subcutaneously and evipan injections are given intravenously four hours and forty-eight hours respectively after the second heroin injection. The average duration of sleep caused in animals of the same age by evipan alone is five minutes.

Average duration of sleep (min.) caused by intravenous injection of 25 δ per g. of sodium evipan in rats having received two successive subcutaneous injections of heroin*

Heroin Dose (δ per g.)	Average duration of sleep caused by evipan: 4 hours after heroin (min.)	Average duration of sleep caused by evipan: 48 hours after heroin (min.)	Controls
4	6	5	5
7	17	12	

*The experiments were performed on groups of five rats and the figures show the average of the results obtained.

The above table shows that small doses of heroin (0.004 mg. per g.) do not affect the average duration of sleep induced by evipan in rats. With a large dose, the increase in the average length of sleep persists when evipan is injected forty-eight hours after two doses of heroin.

(b) *Reaction to evipan of rats habituated to heroin.* Animals injected with increasing doses[20] of heroin receive

[20] The doses increased from 0.01 to 0.1 mg. per g., a daily increase of 0.01 mg. per g.

intravenous injections of evipan sodium four, twenty-four and forty-eight hours after the last heroin injection. Rats of the same age are injected with evipan alone.

Average duration of sleep (min.) caused by intravenous injection of 25 δ per g. of evipan sodium in rats habituated to heroin*

Heroin (δ per g.) last dose before evipan	Time elapsed between injections of heroin and evipan (hours)	Average duration of sleep in habituated rats (min.)	Controls
			5
70	5	12	
70	24	7	
70	48	8½	

* The experiments were performed on groups of five rats; figures are average results.

The increase in the average duration of sleep is smaller if the evipan is injected twenty-four hours after heroin than if it is administered after four hours.

(c) *Summary*. A comparison of the behaviour of normal rats and those habituated to heroin under the influence of evipan shows that the increase in the length of sleep continues for a shorter period in the case of the latter than in the case of the former, despite the injection of a dose of heroin five times greater in the habituated animals than in normal rats. There is, however, no cross habituation.

G. *Summary*

(1) The systematic study of the toleration by rats habituated to morphine of doses toxic to normal rats and of the wearing off of the analgesic effect of the drug indicates that the rat becomes habituated to increasing doses of morphine hydrochloride (0.100 to 0.500 mg. per g.) injected subcutaneously from three to seven weeks (groups II and III).

The 50 per cent lethal doses of morphine hydrochloride injected subcutaneously and intravenously are as follows:

0.250 and 0.100 mg. per g. for the normal rat;

0.800 and 0.165 mg. per g. for the habituated rat.

The ratio of toxicities of morphine hydrochloride, depending on how it is administered, is higher for the habituated rat (4.8) than for the normal rat (2.5) and is close to that obtained with oxydimorphine hydrochloride injected into the normal rat (6.3). Those facts consequently do not invalidate the hypothesis that morphine is converted into oxydimorphine in the habituated animal.

Toleration of toxic doses injected subcutaneously may even be built up very rapidly: after the injection of 0.100 mg. per g. for three consecutive days (group I), the rat withstands a dose three times that of the 50 per cent lethal dose injected subcutaneously for the normal animal. Those rats have the same toleration as rats which have had daily injections of increasing doses for three or seven weeks. Animals injected with increasing doses can withstand for four to five weeks daily doses 100 per cent (0.500 mg. per g.) greater than the 50 per cent lethal dose administered by subcutaneous injection (0.250 mg. per g.) for normal rats.

(2) The analgesic effect of morphine hydrochloride injected intraperitoneally has fallen by 60 per cent eight days after the beginning of daily injections of increasing doses of morphine. At the end of three weeks, it has no effect at all and analgesic action only reappears, and then for a short period only, when a dose is administered five times as strong as that injected intraperitoneally in normal rats (groups II and III).

The weakening of the analgesic effect of morphine is noticeable on the fourth day for a dose three times as strong as the initial dose for rats in group I.

(3) Habituated rats react to hypnotics in very much the same way as normal rats which have had two successive injections of morphine hydrochloride; there is no cross habituation.

(4) Rats injected subcutaneously with increasing doses of heroin (0.010 to 0.100 mg. per g.), withstand a dose ten times stronger than normal animals; the high degree of toxicity, depending on how the drug is administered (subcutaneously or intravenously) in those animals seems to indicate a rapid transformation of the heroin into a less toxic substance, morphine, in the body of animals habituated to the drug. The analgesic effect of an average dose of heroin diminishes after eight days of daily injections. The rat therefore becomes habituated to regular injections of increasing doses of heroin. There is no cross habituation to the action of evipan. Rats tolerate less well repeated injections of regular weak doses of heroin (0.010 mg. per g.). Nevertheless they can tolerate without mortality a subcutaneous injection of a dose 100 per cent stronger than that which would be toxic for the normal animal, and the analgesic effect of heroin becomes weaker in those animals.

(5) If habituation is defined in terms of the normal animal's tolerance of toxic doses and of the disappearance of the analgesic effect of a dose which was originally effective and its reappearance for a larger dose, it may be concluded that the rat is capable of becoming habituated to both morphine and heroin.

All of this work required habituating more than 600 rats.

OFFICIAL

Sixth Session of the Commission on Narcotic Drugs

The sixth session of the Commission on Narcotic Drugs was held at Permanent Headquarters in Manhattan, from 10 April to 24 May 1951. The exceptional length of this session was due to the fact that it had to discuss fully the problem of limiting the production of opium to medical and scientific needs. Because of the importance of the question certain countries were invited to send observers: Belgium, Italy and Switzerland. Burma and Thailand were also represented by observers when the Commission took up the Burmese proposal for the creation of a United Nations committee to deal with the suppression of the cultivation of the opium poppy and of the traffic in opium in South East Asia, where the problem is serious.

At this session the Chairman was Mr. A. N. Sattanathan (India), the Vice-Chairman, Dr. Oscar Rabasa (Mexico), Second Vice-Chairman, Dr. Ali K. Fahmy (Egypt), and Mr. Samuel Hoare (United Kingdom) was the Rapporteur.

The problem of limiting opium production to medical and scientific needs was no longer a problem of principle: the Commission had already accepted this limitation at its fourth session (see: *Bulletin on Narcotics*, vol. III, no. 2) and, in pursuance of previous decisions, a certain measure of agreement had been reached: shares of production for each country, necessity for an international opium monopoly. In addition, there had been a French proposal for an international alkaloids monopoly. However, agreement had not been reached on certain questions, because of the irreconcilable position of various delegations on such questions as the prices at which the proposed monopoly should conduct its opium transactions, the competition from alkaloids manufactured from poppy-straw, the possibility that certain opium-producing countries would start manufacturing and even exporting alkaloids, and the precise form which international inspection should take. These difficulties being apparent from the start of the session, it seemed that the various positions had not evolved towards a possible agreement, but rather that they had become more intransigent; the present world situation indeed seemed to be against—at any rate for the moment—the conclusion of agreements based on an exact price for raw materials and an international inspection system.

The Commission stressed the fact that this situation was temporary in nature, and that the principle of limitation was in no way questioned, nor was the advantage of constituting an international opium monopoly. The Commission, since it faced this deadlock, started exploring other avenues. The French representative then submitted a proposal, which, he contended, might constitute a method of solving this problem which consisted chiefly in adapting to opium the provisions of the 1931 Convention. This proposal provided for:

(1) A system of estimates;

(2) Statistical returns;

(3) Indirect limitation of production and import by means of limiting the opium stocks authorized for each party to the protocol;

(4) Establishment of national opium monopolies;

(5) Control of the non-medical use of opium;

(6) International control permitting imposition of embargoes and local inquiries.

This proposal was discussed at length and the Commission felt that it could not come to a final decision on this plan. It accordingly nominated a Drafting Committee and adopted a text stating that the draft protocol prepared by this Committee "represents a step" in the direction of limiting the production of opium to medical and scientific needs. The text was based on the conception of the maintenance of free competition in the opium trade, and it provided that no country which did not export opium in 1950 should be permitted to export opium in future; the formation of cartels either by purchasers or by sellers of opium was prohibited; no country might hold stocks of opium above a certain maximum level, which was to be fixed by the PCOB. A new provision in this machinery was that whereby a country upon which an embargo had been imposed by the Board might appeal to a specially constituted tribunal. Having adopted these principles on 18 May, the Commission decided, by 8 votes for, 2 against, with 2 abstentions, to recommend to the Economic and Social Council the adoption of a resolution entitled: "Principles of the Proposed Protocol relating to the Limitation of the Production of Opium", reading as follows:

"The Economic and Social Council

"Conscious of the importance of international efforts for the prevention of the development of drug addiction;

"*Considering* that for this purpose effective measures should be taken to further the progress made under the 1925 and 1931 Conventions, in particular by seeking to limit the production of opium to medical and scientific needs;

"*Considering* that present circumstances make the establishment of an international opium monopoly coupled with a monopoly of alkaloids difficult for the time being;

"*Considering* that it is nevertheless desirable to take such measures to further this aim as are practicable at the present time;

"*Adopts* in general the principles of the protocol relating to limitation of the production of opium drafted by the Commission on Narcotic Drugs during its sixth session;

"*Requests* the Secretary-General to submit these principles to the Members of the United Nations and to non-member States parties to the international treaties on narcotics for the communication of their observations thereon before *(date)* with a view to the preparation for the next session of the Council of an annotated compendium of these observations;

"*Decides* to study at an early session, in the light of the observations made, the possibility of convening an international conference entrusted with the task of preparing and adopting a protocol relating to the limitation of the production of opium."

Thus the Commission on Narcotic Drugs, considering the present moment unfavourable to the establishment of an international opium monopoly, sought other means, in view of the circumstances, to work towards its goal, which is the limitation in general and by all means of the production and of the distribution of narcotics to legitimate uses.

The greater part of its time having been thus devoted to the discussion of the limitation problem, the Commission was unable to treat in detail the second major problem in the narcotics field, the proposed Single Convention on Narcotic Drugs intended to replace the eight international instruments (see document E/CN.7/AC.3/3, and *Bulletin on Narcotics*, vol. II, nos. 1, 2) on narcotics. At present the governments represented on the Commission on Narcotic Drugs are considering the Draft Single Convention, and it will not be possible to consider calling an international conference on this matter until they have submitted their observations.

The Commission also studied the questions which regularly come up at each session and which deal with the application of existing Conventions, particularly illicit traffic. In this respect, the Commission examined the question of heroin production in Italy and its diversion into the illicit traffic and, while congratulating the Italian Government on the measures it had already taken for stopping this traffic, it decided to ask that Government to make every effort for the safeguarding of the heroin stocks and to deal firmly with all violations. The question arose of the disposition of seized drugs; the representative of Egypt was of the opinion that the government executing the seizure should be allowed to deal with it as it thought best. However, this view aroused strong opposition—particularly by opium-producing countries—and it was decided to put two alternative solutions to the Council for its decision: either destruction of the seized drugs, or else, conditional disposal of the drugs by the governments.

On the other hand, studying the question of propaganda on the abuse of narcotics, the Commission finally decided that it was a matter for caution and that propaganda and education should be used only in those countries where such abuse was prevalent and this resolution was to be transmitted, if approved, by the Economic and Social Council, to UNESCO.

Finally, the Commission had an opportunity to apply article 2 of the Paris Protocol on synthetic drugs in the case of two new drugs known as "Nu-1932" and "Nu-2206". Those two products are at present being examined by the World Health Organization which will take a final decision as to their likelihood of producing addiction. Pending this decision the Commission has put the above-mentioned drugs under international control.

The Commission has set the second week in April 1952 for holding its seventh session.

Resolutions on Narcotic Drugs Adopted by the Economic and Social Council at its Twelfth Session

In view of the interest presented by the resolutions recommended to the Economic and Social Council and which this organ adopted in their original or amended form, the editors of the *Bulletin on Narcotics* decided to present these resolutions *in extenso* in the Official part of the *Bulletin*.

Report of the Commission on Narcotic Drugs

The Economic and Social Council

Takes note of the report of the Commission on Narcotic Drugs on its fifth session.

Single Convention on Narcotic Drugs

The Economic and Social Council

1. *Approves* the plans prepared by the Commission on Narcotic Drugs for the further elaboration during 1951 and the early part of 1952 of the single convention on narcotic drugs; and

2. *Reaffirms* the authorization given by its resolution 315 (XI) to the Commission on Narcotic Drugs to request the Secretary-General, if the Commission should so desire, to transmit the draft instrument to governments for their comments after making such amendments thereto as it shall have seen fit.

Interim Agreement to Limit the Production of Opium to Medical and Scientific Needs

The Economic and Social Council,

Having considered the efforts of the Commission on Narcotic Drugs and its committees during the years 1949 and 1950 to achieve an effective limitation of opium production to that required for medical and scientific needs,

Being fully aware of the problems involved in this new measure for the more effective control of narcotic drugs, and of the gratifying progress the Commission has already made towards solving them,

Urges the Commission to make every possible effort during its sixth session to find a basis acceptable to the governments principally concerned on which an international agreement to limit the production of opium to medical and scientific needs could be formulated.

Offer for Sale in Hong Kong of Five Hundred Tons of Opium at Present in China

The Economic and Social Council,

Taking into account the present efforts of a number of States to conclude an interim agreement to limit the production of opium to medical and scientific needs,

Considering that China had prohibited the cultivation of the opium poppy and had declared that it did not wish to export opium,

Considering that the draft of the said interim agreement, the general principles of which were approved by the Joint Committee of the Principal Opium-producing Countries and of the Principal Drug-manufacturing Countries during the first part of its first session held in August 1950, is based on the assumption that China will continue to prohibit the cultivation of the opium poppy and the export of opium,

1. *Views* with concern the offer for export of five hundred tons of opium at present in China to which reference is made in document E/CN.7/211; and

2. *Requests* the organs entrusted under the international treaties with the control of narcotic substances to ascertain, if possible, the origin of this opium, the period in which it was collected, the total stocks of opium at present in China and whether the cultivation of the opium poppy and the export of opium are still prohibited in China.

Professor Joseph Perkins Chamberlain

Professor Joseph Perkins Chamberlain, an outstanding figure in international law, who always had a marked interest in the field of international control of drugs, died on 21 May 1951. He was born in 1873, educated at Harvard, at the University of California, etc. He was Ph.D. and LL.D. (Columbia University, Western Reserve University, and University of California).

Admitted to the California Bar in 1902, he practised law in San Francisco from 1902 to 1905 and was lecturer on law at the University of California School of Jurisprudence (1907-1908). He then held various posts in which his ability as a scholar and a man of practical vision attracted attention. He was a member of the Legislative Drafting Research Fund (Columbia, 1909) and Director (1918); Professor of Public Law (Columbia, 1933); Member of the High Commissariat for German Refugees (1933-1935); Chairman of the American Council of Voluntary Agencies for Foreign Service; Chairman of the American Council of Learned Societies; Chairman of the American Bar Association; George Eastman Professor at Oxford University and Consultant for the US Department of State.

He published many erudite books and articles among which an *Index Digest of State Constitutions* (1915); *Régime of the International Rivers: Danube and Rhine* (1923); the *Judicial Function in Federal Administrative Agencies* (1942).

The Editors of the *Bulletin* take the liberty of reproducing part of a letter from the Director of the Division of Narcotic Drugs addressed to Professor Chamberlain's sister, conveying to her the feeling of all those who knew and appreciated him.

"You may perhaps know that one of his most long-standing interests was the struggle against the social evils of addiction to narcotic drugs, and it was in connexion with the international aspect of this work that I first met him in 1932 at Geneva. Ever since that time his wise counsel, stemming from a very deep knowledge and full appreciation of the problem raised by the international control of narcotics, was always available to me for the asking.

"Your brother was never a man to seek the lime-light, being content with painstaking, thorough work in the background and often leaving it to lesser men to take credit that was really his; and it is not yet generally recognized how greatly, as Chairman of the Opium Committee of the Foreign Policy Association, he influenced the American policy which led in large measure to the establishment of the régime for the control of narcotics that now exists throughout the world . . .

"To all of us who are engaged in the international control of narcotic drugs, his death will mean a great loss; to me personally it will mean also the end of a greatly valued friendship. May I convey to you my deepest sympathy . . ."

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SCIENTIFIC PUBLICATIONS ON NARCOTIC DRUGS FOR 1950

INTRODUCTION

The following bibliography has been prepared by the Secretariat and includes scientific publications on narcotic drugs which appeared during 1950, as well as a few which appeared in 1949 but could not, for technical reasons, be included in our list for that year, published in the *Bulletin on Narcotics*, vol. II, no. 3.

This bibliography has no claim to be complete, and information regarding books or articles not included in it would be gratefully received by the Division of Narcotic Drugs, Department of Social Affairs, United Nations Secretariat.

The bibliography has been arranged by subject in the following fashion:

Part I. General and reference works;

Part II. Opium poppy, opium and drugs manufactured therefrom:

- A. (1) Opium poppy, opium and prepared opium;
  - (2) Analysis of opium, its preparations and the determination of its origin;
- B. Morphine;
- C. Other phenanthrene alkaloids and derivatives (under the Conventions);
- D. Other drugs and substances derived from the opium poppy;

Part III. The coca leaf and drugs manufactured therefrom;

Part IV. Cannabis and its derivatives;

Part V. The synthetic drugs:

- A. General works;
- B. Pethidine and related compounds;
- C. Methadone and related compounds;
- D. Morphinan and morphine synthesis;
- E. Other synthetic analgesics;

Part VI. Addiction to narcotic drugs.

Under each heading, publications are arranged alphabetically by author. Due to the nature of the sources available to the Secretariat for preparing this bibliography, several of the titles are given in translation only. They are preceded by an asterisk.

Part I

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ADDICTION TO NARCOTIC DRUGS

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